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Part I.—Original Articles.

THE INHERITANCE OF NEUROTICISM: AN EXPERIMENTAL STUDY.*

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(1) INTRODUCTION.

It is commonly believed that heredity plays a considerable part in the determination of an individual's personality. If we accept the well-known definition of personality as "the integrated organization of all the cognitive, affective, conative and physical characteristics of an individual as it manifests itself in focal distinctness to others," we might expect that much research endeavour would have been dedicated to the discovery of hereditary influences on the cognitive, affective, conative and physical characteristics of the individual. A certain amount of such research there has been, but its emphasis has been curiously lopsided; we have some studies into inheritance of physical characteristics, and numerous studies into the inheritance of cognitive characteristics, but there has been little worth-while research into the conative and affective sides of personality.

The most favoured method of investigation has been the so-called "twin-method" developed in Germany (Siemens, 1924), which consists in comparing the average resemblance of identical twins with that of fraternal twins. The difference between identical twins, due to environment alone, is compared with the difference between fraternal twins, due to both heredity and environ-

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ment ; if differences between fraternal twins are much greater than between identical twins, heredity appears to be a powerful causative factor, while if differences are small or non-existent, the influence of heredity as a causative factor in individual differences is discounted. It is possible to give mathematical expression to the estimated contribution of heredity and environment to the variance of any given test, as well as of the interaction of heredity and environment (Shuttleworth, 1935), provided we are ready to make the assumption that the environment is as similar for a pair of fraternals as for a pair of identicals.

The large amount of research done along these lines into the inheritance of intelligence has been summarized adequately by Verschuer (1939), Schwesinger (1933), Newman, Freeman, and Holzinger (1937), Gottschaldt (1939), and Woodworth (1941). The fairly universal conclusion has been that " inter-family environmental differences account for a much smaller proportion of the variance in intelligence than do hereditary differences " (Shuttleworth, 1935). No equally comprehensive generalization has hitherto been made in the affective and conative fields if we except the rather negative conclusions arrived at by Newman, Freeman and Holzinger (1937) who say : " In most of the traits measured the identical twins are much more alike than the fraternal twins, as indicated by higher correlations. This is true of physical dimensions, of intelligence, and of educational achievement. *The only group of traits in which identical twins are not much more alike consists of those commonly classed under the heading of personality.** . . . The difference in resemblance of the two classes of twins is not the same in the different groups of traits. In general, the contrast is greater in physical traits, next in tests of general ability (intelligence), less in achievement tests, and least in tests of personality or temperament. In certain instances, viz. . . . tapping, will-temperament and neurotic disposition, the correlations of identical twins are but little higher than those of fraternal twins."

A brief review of such experimental and observational data as are available will indicate some of the reasons for this failure to achieve positive results comparable to those achieved in the cognitive field, and will also make us familiar with certain dangers in twin research which have invalidated many conclusions confidently drawn from methodologically inadequate data.

(2) Review of Literature.

Much the most extensive work on the inheritance of personality has been done in the field of mental illness, where twin studies of psychotic (and occasionally neurotic) patients have been widely accepted as a method for elucidating the influence of heredity on pathology. The work of Rüdin (1930), Rosanoff *et al.* (1935, 1941), Essen-Moeller (1941), Luxenburger (1928, 1930, 1933, 1934, 1935, 1940), Kallmann (1941, 1946) and Kallmann and Barrera (1942) leaves little doubt that concordance in identical twins is considerably more frequent than in fraternal twins, although still far from perfect. This type of work inevitably suffers from the subjectivity of psychiatric diagnoses, and the lack of reliability associated with all rating methods.

* Italics not in original.

A quite different field, which also has attracted some attention, is that of criminal tendency. Lange (1931), Stumpfl (1936), Kranz (1936) and Borgstroem (1939) have shown that identical twins are more concordant in their criminality than are fraternal twins, even when complete separation has taken place. Popenoe (1936) concludes from a review of this material that "we must ascribe to heredity a more important role in the production of crime than has hitherto been the case."

When we come to the more definitely experimental type of study, we find that the relevance of the experiment to the question of heredity of personality is usually contingent on the theory of personality held by the investigator. Conditioning experiments appear important to the followers of Pavlov; eidetic imagery to those who agree with Jaensch's system; handwriting is studied by the "expressive movement" school; autonomic patterns are investigated by the physiological experimenters; perseveration and fluency by the Spearman school; projective techniques are employed by the followers of Rorschach and Freud.

Much work has been carried out in the field of handwriting, both along subjective, interpretative lines and along objective, quantitative lines. The picture is somewhat confused. Bracken (1940*a* and *b*) found no hereditary determination for differences in handwriting pressure in 42 pairs of twins, while Carmena (1935*b*) and Miguel (1935) came to the opposite conclusion after experimenting on 50 pairs of twins each. Writing speed was found to be determined largely by heredity in Bracken's (1939*a*) study of 38 sets of twins, a conclusion confirmed in a later study by the same author (Bracken, 1940*a*) on 42 pairs of twins. Thelen (1939) conducted matching experiments which showed hereditary factors to be prominent in handwriting, while Hartge (1936) found handwriting to be of no diagnostic value in individual diagnosis of monozygoticity. Nicolay (1939) and Hermann (1939) agree in finding little hereditary determination in handwriting, with the exception of the writing angle. Saudek and Seeman (1932, 1933) emphasize both heredity and environment in the determination of writing and drawing. Newman, Freeman and Holzinger (1937) support Galton's original finding that there is surprisingly little resemblance between handwritings of identical twins. The one exception to this appears to be the quality of the handwriting (*cf.* also Kramer and Lauterbach (1928)).

Closely related to handwriting studies are three investigations of the Downey Will-Temperament test, which is based essentially on handwriting characteristics. Tarcsay (1939) reports negative conclusions, while Bakwin (1930) is more positive. Freeman, Newman and Holzinger (1937) report findings which definitely disprove the hypothesis that heredity determines individual differences in reaction to this test; the intraclass correlations on the four scales of this test are higher for fraternal than for identical twins! (The actual values are ·69, ·36, ·53 and ·51 as against ·45, ·31, ·51 and ·48.)

Perceptual factors in the personality of twins have been studied by Bracken (1939*c*), Hofstetter (1948) and Smith (1949). Eidetic imagery, which, according to Jaensch's theories is closely connected with personality type, was shown by the last-named author to be strongly determined by hereditary factors, as

was also reaction time. The other authors show that in the production of after-images, in the extent of visual illusions, and in accommodative convergence heredity plays a powerful part.

A beginning has been made in the study of conditioning in twins by Kanaev (1934, 1938, 1941), who used the Krasnogorsky modification of Pavlov's method to show remarkable similarities between identical twins. He links this approach to Pavlov's theories of personality, which are based on conditioning experiments, and it is unfortunate that his suggestive work has been left in a relatively undeveloped state, where no certain conclusions can be drawn.

Another physiological variable which has been studied on the hypothesis that it might be found to be correlated with personality differences is the brain wave pattern. Lennox *et al.* (1945), Elmgren (1941), Davis and Davis (1936) and Gottlober (1938) have shown remarkable similarities between identical twins and less marked similarity between fraternal twins ; in the absence of any satisfactory theory linking brain-wave patterns to personality, however, it is difficult to interpret these findings.

Of more definite relevance to personality are three studies of yet a third physiological variable, viz. the psycho-galvanic reflex. The important monograph by Wenger (1948) has definitely established the close connection between neuroticism and autonomic imbalance, and has shown that the P.G.R. is a good measure of autonomic imbalance. Carmena (1934, 1935*a*), working on 60 pairs of twins, showed that the P.G.R. is strongly influenced by heredity. Jost and Sontag (1944) supported this finding by using, in addition to the P.G.R., pulse pressure, salivation, heart period, respiration rate, vasomotor persistance time, and other autonomic measures. They conclude that an autonomic constitution may be at least partially inherited.

Ratings along the lines of the Vineland Social Maturity Scale have been carried out by Bracken (1939*b*), Troup and Lester (1942), and Wilson (1941) ; there is considerable agreement that whatever is measured by this scale is influenced to a considerable extent by heredity. While it is believed that the Social Maturity Scale measures personality factors additional to intelligence, it has not hitherto been possible to identify them, and therefore it is difficult to interpret the findings.

Motor skill has been studied by Brody (1937) and by McNemar (1933). Both authors find identical twins much more alike than fraternal twins, and conclude that the hereditary hypothesis is the most plausible explanation of individual differences in motor skills. This finding is relevant to personality research because it has been shown by Eysenck (1947) that motor skills correlate quite highly with neuroticism, so that hereditary determination of individual differences in skill gives presumptive evidence for hereditary determination of individual differences in neuroticism.

Related to this work are the studies by Becker and Lenz (1939) and Pauli (1941) showing that differences in work curves are more pronounced in fraternal than in identical twins. Irregularities in work curves have also been shown to be diagnostic of neuroticism (Eysenck, 1947), so that this finding, too, supports the tentative hypothesis that neuroticism may be based on an hereditary foundation.

Perseveration has been studied by Yule (1935) and by Cattell and Molteno (1940). The former, using 115 twins, showed that on a battery of p tests of Stephenson type heredity played an important part ; the latter, using 84 pairs of twins, found that p tests gave no evidence of hereditary influence. Tests of F (fluency of association) were also given by Cattell and Molteno, who concluded that family-environmental differences " are about 8 times as important as hereditary segregation of genes in accounting for individual differences in fluency." This conclusion links up with the work of Carter (1938, 1939) and Sorensen and Carter (1940) on association in twins ; it was found that identical twins are slightly more alike with respect to speed of association.

Most of the studies mentioned so far have had only tangential relevance to personality ; more directly relevant might be work on questionnaires and projective tests. Carter (1933, 1935) has reported on the use of the Bernreuter Personality Inventory as applied to 133 pairs of twins. Identical twins were markedly more similar than fraternal twins with respect to neurotic tendency, self-sufficiency and dominance. This conclusion does not agree with the results published by Newman, Freeman and Holzinger (1937) with respect to another neuroticism questionnaire. The Rorschach technique has been used by Troup (1938), Eckle and Ostermeyer (1939), Marinescu *et al.* (1934), and Kerr (1936). Results are conflicting, Kerr's being essentially negative, Marinescu's positive, while the other reports are somewhat intermediate. No clear picture emerges from the combined results, however.

Certain techniques have been used by one investigator only, and while the connection between the test used and personality is not always clear, the results illustrate a point in methodology which we want to stress in the discussion. Szondi (1939) found greater similarity in identical twins when he applied the test that bears his name to 97 pairs of twins. Petö (1946) used psycho-analysis as his method of investigation, finding surprising identity of symptom in two identical twins. Malan (1940) found spatial orientation to be an inherited trait. Hunt and Clarke (1937) showed marked differences in the startle pattern of a pair of twins. Carter (1932) found occupational interests to be due in part at least to hereditary causes. Frischeisen-Köhler (1933) reports that personal tempo is definitely conditioned by heredity. Thompson (1943) showed determination of play-behaviour by heredity. Waardenburg (1929) shows greater similarity between identical twins with respect to likes and dislikes. Zilian (1938) found less variability for identical twins on imaginal and motor factors. Steif (1939) found great similarity in scribbling between identical, little similarity between fraternal twins, a result similar to Luchsinger's findings with respect to voice range (1940).

Certain obvious characteristics emerge even from this very brief review of the literature dealing with twin studies in personality research. (1) Objectively oriented investigations are mostly very limited in scope, dealing with traits of a low order of complexity, such as scribbling, angle of handwriting, eidetic imagery, reaction times, or spatial orientation. (2) When an attempt is made to study higher-order concepts, such as criminality or psychosis, the concepts chosen are of a sociological-ethical, or psychiatric rather than of a psychological nature, and the investigation proceeds along lines far removed

from the objectivity of psychometric testing procedures. (3) While on the whole most authors agree that identical twins are more alike than fraternal twins on most of the tests used so far, there are many inexplicable contradictions (e.g. the studies of perseveration, of questionnaire tests, and of the Rorschach). (4) Most personality tests have such low reliabilities that results are almost bound to be disappointing ; correction for attenuation is seldom attempted. (5) Even when results are clear-cut, they are often difficult to interpret, due to our lack of knowledge of precisely what it is a given test is measuring.

Some of the conflicting results reported may be due to technical faults, which vitiate many of the studies reported. Results are often stated as impressions, rather than being reported as objectively scored and statistically validated conclusions. Choice of twin-pairs to be tested is often based on faulty sampling practices, fraternal twins which look unlike each other being overlooked in favour of those who resemble each other. (Correct procedures are suggested by Verschuer (1939) and Rosanoff *et al.* (1937)). Diagnosis of monozygoticity or dizygoticity has often been faulty, even where the procedures adopted have been described in full. These and other technical faults are easily overcome by experimenters of reasonable competence. Two other criticisms are more fundamental, and must be discussed in some detail.

(1) In passing, we have noted that the whole procedure of twin research rests on the assumption that the environment is as similar for a pair of fraternal twins as it is for a pair of identical twins. Stocks (1930), Holmes (1930), Bracken (1933, 1934*a*, 1934*b*, 1935, 1936), Wilson (1934) and Jones and Wilson (1933) present reports indicating that identicals are treated more alike than are fraternals, a fact which would appear to invalidate this assumption. Bluekersken (1935), Lohmeyer (1935), and Misbach and Stromberg (1941) on the other hand, show that often the very fact of the identicals' similarity leads to different development in the sense that they take on complementary roles. Schiller (1937) and Newman *et al.* (1937) have confirmed this point. Meumann (1935) and Bouterwek (1936) have shown a tendency for identical twins to select different occupations. Woodworth (1941) comments that " such differentiations of roles as has been observed would probably cause identicals to differ in certain special abilities and personality traits . . ." In any case, as Wilson (1934) has emphasized, while in many respects the identical pairs live under more similar conditions than the fraternals, " this fact must be attributed ultimately to the influence of their heredity which led, or forced them to ' select ' more similar environments." While it is impossible to be dogmatic on this point, it does appear that the argument against similarity of environment for the two types of twins is speculative and hypothetical ; there is no evidence to suggest that such differences as may exist are not themselves due to hereditarily determined selection of environments, or that the small differences observed could account for the large differences in test results. Until more empirical evidence is produced by the critics we cannot concede that their arguments do much damage to twin research methodology.

(2) This criticism of twin work has not, to our knowledge, been made previously, although a solution to the problem posed by it has been published

elsewhere (Eysenck, 1950). It is relevant not only to studies of temperamental traits, but equally so to work on intelligence, and would seem to undermine the elaborate structure of argument built up on twin research. Essentially, this criticism concerns a conceptual jump which takes place when an argument is presented regarding the inheritance of *intelligence* from the intercorrelations of identical and fraternal twins on a *particular test*, say the Binet. We may generalize and say that *a demonstration that individual differences in performance on a given test are due to heredity cannot be used as proof that a hypothetical trait or ability imperfectly measured by that test is inherited.* The argument can best be presented by using an algebraic model.

We may write the factorial equation of the Binet test in the following form :

$$\sigma^2_{BINET} = \sigma^2_g + \sigma^2_V + \sigma^2_N + \sigma^2_{SP} + \sigma_M + \sigma^2_C + \ldots + \sigma^2_X + \sigma^2_S + \sigma^2_E$$

where σ^2_{BINET} denotes the total variance of the Binet test, σ^2_g the contribution to that total variance made by "*g*" or intelligence, while σ^2_V, σ^2_N, σ^2_{SP}, σ^2_M, $\sigma^2_C \ldots \sigma^2_X$ denote contributions to the variance by verbal, numerical, spatial, memory, comprehension and other group factors, and σ^2_S and σ^2_E stand for the contribution to the variance of specific and error factors. Using estimates derived from Burt and John's (1942) analysis of the Binet, the total variance contributed by "*g*" or intelligence is only about 30 to 40 per cent., or less than half the non-error variance. McNemar's (1942) series of analyses attributed on the average 40 per cent. of the total variance to "*g*", the proportion ranging from 35 to 50 per cent. If we neglect the error variance, which amounts only to about 5 per cent. and, of course, cannot be said to be caused either by heredity or environment, but which is merely an error of measurement uncorrelated with the abilities or traits the test is measuring, we can conclude by and large that one-half of the variance at most is due to "*g*" while at least one half is due to various other common factors or specifics.

It will be clear now how unjustified is the jump from the statement "Individual differences in Binet scores are accountable for in terms of heredity to the extent of 80 per cent.," which, granted certain assumptions, is a statement of fact, to the much more usual statement that "Individual differences in intelligence are accountable for in terms of heredity to the extent of 80 per cent.," which is a completely unwarranted generalization, which could be made only if all the non-error variance were attributable to "*g*." It could be that all the group and specific factors hypothesized were completely determined by heredity in which case heredity would play only a very minor part in the determination of "*g*"; it could be that the group and specific factors were largely caused by environmental differences, in which case "*g*" might be 100 per cent. inherited. *Unless we can analyse the total variance of a test into its constituent parts, and measure these parts separately, no scientifically tenable conclusion can be drawn from the data.* If this criticism be justified, it follows that the whole literature on the inheritance of intelligence, perserveration, social maturity, motor skill, conditionability, personality type, or any other ability or trait, in so far as it is based on twin studies, must be considered invalid. This conclusion may appear harsh in the extreme, but it is difficult to see how it can be avoided on the evidence to hand.

(3) The Experimental Variable: Neuroticism.

It follows from what has been said above that if we want to measure the degree to which a particular trait or ability is inherited in a given sample, then we must study, not the individual test results, but rather the hypothetical underlying factors which generate the test variance. In studying intelligence this would mean administering a battery of tests to the experimental population, intercorrelating these tests, factor-analysing the resulting factor matrix, and obtaining factor scores for each experimental subject on each factor isolated. We could then submit these factor scores to the mathematical treatment appropriate to our problem, and obtain data relevant not to one test only, but to intelligence, or verbal ability, or memory, or whatever our factors might turn out to be.

In the field of cognition, the main factors underlying test performance have been isolated by Spearman, Thurstone, Holzinger and other experimenters using the method of factorial analysis. We know now what to measure, and we know how to measure it. In the fields of conation and affection, however, the position is less clear. There are numerous theories, but few facts; much is hypothesized, but little known. The problem thus arises as to the correct choice of the experimental variable.

Our choice has been determined largely by two considerations: (1) The social importance of the trait investigated and (2) the existence of a sufficient body of knowledge regarding it. On both counts, we had little difficulty in arriving at our decision to study the inheritance of the trait variously named neuroticism, emotional instability, or lack of integration. This trait is conceived of as a personality variable ranging from the extremely stable nature, well integrated and through the average sort of personality to the extremely unstable, poorly integrated, neurotic type of individual. The population is conceived of as lying along this continuum, so that everyone can be assigned a "neuroticism score" which would specify his exact position. The distribution of people on this continuum is believed to be unlikely to deviate far from the normal type of curve which characterizes the distribution of scores on intelligence tests.* On this hypothesis a neurotic group would contain in the main people with very high neuroticism scores, while an unselected group would contain people with both high and low scores, but predominantly those with medium scores.

The hypothesis outlined above was originally advanced as the result of a factorial study of personality ratings made by a group of psychiatrists on 700 neurotics (Eysenck, 1944). Much evidence has been published since to show that this hypothesis leads on to various deductions which can be confirmed experimentally, thus strengthening the belief in its usefulness (Eysenck, 1947). In particular a new method of analysis, called "criterion analysis," has been elaborated to deal with hypotheses of continuity of normal and abnormal groups (Eysenck, 1950), and its application has added further proof for the essential correctness of the original hypothesis. These methods have been applied to data gathered through the use of objective psychological tests

* The actual form of distribution is irrelevant to the argument.

(Eysenck, 1951*c*), and batteries of tests have been constructed and used for the more detailed investigation of this trait of "neuroticism" (Himmelweit and Petrie, 1951).

Other traits investigated in a similar manner include Jung's conception of extraversion-introversion as a dimension of personality (Eysenck, 1947) and Kretschmer's hypothesized traits of schizothymia and cyclothymia (Eysenck, 1951). While these traits were considered at an early stage of the experiment, it was decided that too little experimental material was to hand to justify us in constructing a test battery for them, and it was also felt that from the point of view of social relevance neuroticism probably had a higher claim.

We may now state the hypothesis investigated in this paper in a formal manner: The trait of neuroticism, as operationally defined in terms of the pattern of intercorrelations between a specified set of objective personality tests, is in large part determined by heredity, and such individual differences with respect to it as appear in the experiment cannot be accounted for in terms of environmental influences.

The relevance of the experiment to the psychological and psychiatric fields needs little stressing; it may be worth while, however, to point out the importance attaching to the result from the point of view of the logic of factorial analysis. It will have been noted that our definition of neuroticism is essentially in terms of factorial analysis, i.e. in terms of the condensation of a set of observed correlations into a similar number of hypothetical underlying variables or factors. This method has frequently been criticized on various grounds, and while some of these criticisms have not always been based on thorough knowledge of precisely what is implied in the method, it cannot be gainsaid that some doubts could not be allayed in terms of statistical arguments alone. In particular, the fact that the resolution of a given matrix of intercorrelations into factors can be carried out in an infinite number of ways has perplexed many critics otherwise not hostile to this approach. Thurstone's method of overcoming this difficulty (a difficulty which is not faced at all by some writers, *e.g.* Burt and Stephenson) is well known; it consists essentially in overdetermining the solution. This method, while of the utmost importance in work on abilities, appears less well suited to the requirements of non-cognitive experimentation, and the method of "criterion analysis" has been suggested as a plausible alternative (Eysenck, 1950).

However, proof has been lacking hitherto that factors thus determined have any "real" existence, and are something other than mere "statistical artefacts." In part the argument about "real" existence is, of course, a philosophical and semantic one; in a very definite sense any scientific concept is an "artefact" lacking "real" existence. A concept, whether it be that of an electron, an instinct, a quantum of energy, a complex, or a sound wave, is an abstraction, and thus not "real"; scientific concepts are "artefacts" almost by definition. However, what critics usually mean by this objection is something quite different. They denote a factor an "artefact" if it does no more than merely to summarize existing knowledge, if it does not go beyond the circle of its own derivation.

Here the present experiment should be of crucial importance. Having

defined our factor of neuroticism in terms of the intercorrelations of a set of tests, we proceed to examine the biological unity of this factor by analysing the degree to which the factor *as a whole* is inherited. The crucial question, therefore, is this: Is the degree of hereditary determination of this factor greater than that of any single test contributing to the total factor variance, or is nothing gained by substituting the " factor score " for the score on any of the tests which jointly define the factor? If the result shows that the factor is inherited to a more marked extent than any single test, it follows that we have succeeded in proving that the factor is no mere artefact, but has a certain degree of biological reality. As will be shown later, the considerable difference actually observed in hereditary determination between factor and best test encourages us to believe that we have succeeded in its demonstration.

(4) Experimental Study.

(a) *Selecting the Sample of Twins.*

In any study involving a comparison of identical and fraternal twins, care must be taken to avoid errors that might arise from unrepresentative samples. Many previous studies have been open to criticism because of their methods of sampling. If the selection of twins is carried out as in the study of Newman, Freeman and Holzinger (1937), by inquiry into local schools, there exists the possibility of overlooking those fraternal twins who are quite dissimilar, thus yielding an underestimate of the average difference between fraternal twins. This is because twins who are much alike attract attention and are brought to the investigator's notice, while those differing considerably in appearance and behaviour may be overlooked. The questionnaire method of sampling is even more likely to yield a sample overloaded with fraternal twins who are very much alike. Probably the most adequate method of securing an unbiased sample is to use the birth record method (von Verschuer, 1940). This was the method used in the present study.

The birth records for five boroughs in South London were searched for all twins of the same sex, born during the period 1935–1937. The reason for selecting only like-sex twins was that identical twins of necessity belong to the same sex. If, then, fraternal twins of the opposite sexes had been included, they would have introduced a possible complication due to sex differences. Concerning the age limits, the lower limit was set because children younger than 11 could not have taken all of the tests; the upper limit was set because a wide age-range necessitates statistical corrections for age which complicate the picture.

The survey of the birth records yielded the names of 130 pairs of like-sex twins. From these it was possible to locate 68 pairs who were living in the London area, close enough to be able to attend the Psychological Laboratory of the Institute of Psychiatry. The remainder were either living too far away, had died, or could not be located. In no case was parental permission to test refused. The twins were examined as they were located. After examination they were classified as identical or fraternal according to a procedure to be described in the following section.

Methods of Diagnosing Monozygotic and Dyzygotic Twins.

Although there is no longer any doubt of the existence of two types of twins efficient criteria are needed in order to effect a valid separation in all cases. Two methods of diagnosis have been used to group identical and fraternal twins—the foetal membrane method and the similarity method. In view of the many criticisms made of the former, the latter was employed.

The similarity method involves the comparison of the members of a pair of twins in respect of numerous physical characteristics which are determined by heredity. As the number of characteristics is increased arithmetically, the chances of any two siblings not being alike on all the characteristics is increased geometrically. Therefore, if the chances of two children in the same family being alike in one such characteristic is one in two, the chances of their being alike in ten is one in one thousand.

In the present investigation the set of criteria upon which the diagnosis of zygoticity was made is as follows :

(1) Close resemblance of ears, teeth and facial features.
(2) Iris pigmentation.
(3) Standing height.
(4) Presence or absence of mid-digital hair.
(5) Ability to taste phenyl-thio-carbamide.
(6) Scapular shape.
(7) To (14) blood groups A_1A_2BO, Rh, MNS, P, Lewis, Kell and Lutheran.

(1) Close resemblance of ears, teeth and facial features was rated on a three-point scale : No resemblance, different (D) ; pronounced resemblance, but slight differences (SD) ; and very pronounced resemblance rendering it almost impossible to distinguish the twins, same (S).

(2) The *resemblance of the iris pigmentation* was rated on a three-point scale : No resemblance, different (D) ; pronounced resemblance, but slight differences in one zone (SD)* ; and very pronounced resemblance, rendering it almost impossible to distinguish the twins, same (S).

(3) The *standing height* of each twin was measured to the nearest quarter of an inch.

(4) *Presence or absence of hair* on the dorsum of the mid-digital region of the fingers was determined by placing the subject's hand, half clenched and bent slightly backwards, between the investigator and a source of light. This was provided by a 100-watt electric light placed 7 ft. behind the subject's hand. Presence of any hair on one or more fingers was scored as : *hair* +.

(5) *Ability to taste phenyl-thio-carbamide* was ascertained by having the subject drink one-quarter teaspoonful of a 1/20,000 solution of PTC. The subject was asked what the substance tasted like. Any answer other than water was scored as : *taste* +.

(6) The *scapular shape* was found by running the hand over the inside edge of both scapulae. The twins were classified as either concave (CC),

* In the majority of individuals, the iris is composed of two zones, an inner and an outer of different pigmentation. In fifty pairs of siblings studied by Rife (1943), no two pairs were found to have the same iris pigmentation in regard to both zones, although in ten pairs the outside zones were the same, and in four pairs the inside zones were the same.

straight (S) convex (CV), or mixed (M). The mixed type included any combination of the other three : (CC–CV), CV–S), etc.

Grouping the Twins into MZ and DZ.

Using the data on the 14 criteria the twins were first classified into one of three groups : definite MZ, definite DZ and doubtful. The application of criteria for the initial grouping of the twins is shown in Table I.

TABLE I.—*Application of Criteria for Initial Grouping of Identical and Fraternal Twins.**

Criterion number.	Definite MZ.	Doubtful.	Definite DZ.
(1) and (2)	(S) and (S)	(SD) and (SD) or (S) and (SD) or (SD) and (S)	(D) and (D)
	and	and	or
(3)	Difference 1·5 in. and	Difference 3·5 in. and	Difference 3·5 in. or
(4) to (14)	All exactly alike	All exactly alike	Different on any one

* See Text for Explanation of the Table.
(S) Same ; (SD) slight difference ; (D) different.

A pair of twins was considered definite MZ if they had (S)'s in criteria (1) and (2) ; differed less than 1·5 in. in height on criteria (3)* ; and if the children agreed exactly on criteria (4) to (14) inclusive. Twins were considered as definite DZ if they were rated (D) on both criteria (1) and (2) ; *or* if their height differed by more than 3·5 in., criterion (3) ; *or* if they differed on any one of criteria (4) to (14) inclusive. Twins were considered doubtful if they had ratings of (SD) on both criteria (1) and (2), or a rating of (SD) on either (1) or (2) and a rating of (S) on the other ; if they differed 3·5 in. or less on criteria (3) ; and if they agreed exactly on criteria (4) to (14) inclusive.

On the basis of the above procedure, 20 pairs of twins were classified as definite MZ, 24 pairs as definite DZ, and 6 pairs as doubtful.

When a pair of twins had been rated as doubtful, the blood groups of both parents were ascertained in order to effect a final classification.† The blood

* Newman, Freeman and Holzinger (1937) found that 94 per cent. of their 50 sets of MZ twins had pair differences in standing height of less than 1·5 in. ; 53·8 per cent. of their 50 pairs of DZ twins had pair differences of less than 1·5 in. None of their MZ twins had a pair difference of over 3·1 in. ; whereas 19·1 per cent of their DZ twins had a pair difference of over 3·1 in.

† Blood group tests were not made for the parents of all 50 pairs of twins, as it was feared that an attempt to persuade the parents to submit to a "blood-test" might have resulted in a loss of the co-operation already secured.

groups of the twins and their parents were then compared to determine the chances of the blood groups of two siblings from a known mating being alike on all of the blood groups. In five of the doubtful pairs, the chances of the two children being alike on all of the blood groups, taking into account the blood groups of their parents' blood, were : 1 : 256, 1 : 256, 1 : 1,000, 1 : 1,000 and 1 : 2,000. Accordingly, these pairs of twins were classified MZ. In the other doubtful pair the chances were : 1 : 16, therefore this set was classified DZ.

(b) *Selecting the Sample of Neurotics.*

The research design calls for a criterion group of neurotic children against which the factor extracted from the normal twins could be validated. Twenty-one children born between 1935–1937 were selected from out-patients at the Maudsley Child Guidance Clinic. Great care was taken to exclude children with organic complications, or with possible psychotic traits, or who were not definitely considered " unstable " by the examining psychiatrist. The resulting sample of 21 children approaches as closely as is possible at the present stage of psychiatric knowledge a " pure " neurotic group, with relatively little mixture of other mental or physical disorders.

(c) *Tests Used.**

1. *Intelligence.*

The Similarities and the Digit-Symbol Sub-Test of the Wechsler Bellevue Intelligence Scale were given and scored according to the author's instructions.

(2) *Tapping Area.*

The subject is given a sheet of 10 in. × 8 in. blank white paper, which is held down to the table by a frame ; he is then told " This is a tapping game. When I say ' Go,' tap this paper with the point of your pencil as fast as you can. Keep tapping on the paper until I say ' Stop.' Ready. Go." Two 10-second trials are given, one immediately after the other, the paper being turned over to the clean side for the second trial.

Scoring is in terms of the perimeter (in inches) of the area generated by the dots on the test paper, only convex lines being allowed in drawing the perimeter.

(3) *Speed of Tapping.*

An automatic counter is fastened to a table in such a way that the subject standing in front of the counter cannot see the window where the number of taps is recorded. The subject is instructed to tap on the counter as quickly as possible and the experimenter records the number of taps per 10-second period.

(4) *Level of Aspiration.*

A level of aspiration procedure is incorporated with the previous test in such a way that the subject, once he is familiar with this, states his aspiration for future trials and his judgment of past trials. Final score on the test is the affective discrepancy score as described in detail elsewhere (Eysenck, 1947).

* This investigation was planned in 1947, and consequently our choice of tests was made on the basis of our very incomplete knowledge then. To-day this choice could be much improved.

(5) *Motor Speed Test.*

The subject is required to trace an irregular path marked out between rows of holes with a metal stylus on the track tracer. Every time he touches a hole a buzzer rings. Instructions are to trace this path as accurately and quickly as possible ; score is the time in seconds taken to trace the path to the centre.

(6) *Speed of Decision.*

A pack of 52 playing cards was used in this. The experimenter places two cards face downwards before the subject and gives the following instructions : " Now we will play a game of chance. I want you to guess which of these is the higher. You don't know and I don't know—it is just a guessing game. As soon as you have decided, put your finger on the card you think is the higher and as you put your finger on the card I want you to say either ' certain ' or ' uncertain.' If you are certain and you are right, you win two points, but if you are wrong you lose two points. If you are uncertain you can only win or lose one point." A practice trial is given and when instructions are fully understood, 10 trials are given which constitute the test. The time to the nearest half second is recorded from when the second card is placed down to when the subject's finger touches the card. The average of these reaction times on the 10 experimental trials constitutes the score.

(7) *Static Ataxia.*

This is a test of the amount of body sway present during 30 seconds while the subject is standing upright with his eyes closed and his heels together. The score is the amount of sway.

(8) *Body-sway Suggestibility.*

In this test the score is the amount of body sway induced by means of a record which repeats for 2½ minutes " You are falling, you are falling forward, you are falling forward now," etc.

These two tests are described in detail elsewhere (Eysenck, 1947).

(9) *Strength of Grip.*

A hand dynamometer was used in order to measure the strength of grip of the subject.

(10) *Word Dislikes.*

A list of 30 words, given below, is shown to the subject, who is asked to read them out aloud to the experimenter. The subject is asked to put an L after each word liked and a D after each word disliked. The test score is the number of words disliked by the subject.

Lift — Crowd	— Night	— Dreams	— Bed
Train — Water	— Thunder	— Moon	— Dark
Boy — Stranger	— Girl	— Man	— Woman
School — Teacher	— Lesson	— Book	— Number
Father — Mother	— Sister	— Baby	— Brother
Dog — Cat	— Spider	— Mouse	— Rat

(11) *Personality Inventory.*

This is a revision of the Brown Personality Inventory for children given in the form of 32 cards, each with a statement printed on it. These have to be put in a box divided into two sections marked "True" and "False" respectively. The score is the number of symptoms to which the subject answers "Yes."

(12) *Lie Scale.*

In addition to the 32 cards of the above test, four cards were added containing items from the M.M.P.I. Lie Scale, which give another score purporting to show the tendency of the subject to give truthful answers.

(13) *Autokinetic Movement* and (14) *Autokinetic Suggestibility.*

In a completely dark room the subject is shown a very small source of light (stationary). He is asked by the experimenter: "Look in front of you and above the level of your eyes. What do you see?" After the subject states that he sees a little light, say, "Tell me all about it." If the subject reports movement before three minutes, the light is turned off and (*a*), (*b*) and (*c*) are proceeded with immediately. If there is no report of movement at the end of three minutes, the light is turned off and (*a*) and (*c*) are proceeded with, omitting (*b*). If, during the three minute period, the subject stops describing the light the experimenter may say, "Tell me more about it," or "What else can you tell me about it."

(*a*) The flashlight is turned on. "Here is a drawing board and a pencil. In the centre of the board is a drawing pin. I want you to start with your pencil point against the pin and trace the path of the directions in which the light moves."

(*b*) "Thus, if the light appears to move upwards, move your pencil up on the drawing board, or if the light moves to the right, move your pencil to the right. In this way you will be able to record the movements of the small light. If you find that you have reached the edge of the drawing board, return to the centre and continue as before. Otherwise keep your pencil point on the board the whole time. Thus, start from the centre pin and record the movement of the small light. Only remove your pencil from the board if you reach the edge; in this case start again from the centre." The flashlight is turned out and the little light turned on again. "There is the light. Start now." At the end of three minutes the small light is turned off and the subject is handed the red pencil, with the words "Here is another pencil."

(*c*) "The light is going to move down, and I want you to draw it exactly as you see it." If after (*b*) the small light is turned on and the experimenter says, "Start now." If (*b*) has been skipped, the flashlight is turned off, the small light is turned on, and the experimenter says "Start now." The small light is turned off after 30 seconds.

Scoring.—(*b*) Test 13—the length of the line in inches. In case of no movement reported the score is 0.

(*c*) Test 14—if the line is more than $\frac{1}{2}$ in. long *and* the length of the down-

TABLE II.

	Zygotiticity.	Sex.	Age.	Intelligence.	Tapping area.	Tapping speed	Level of aspiration.	Motor speed test.	Speed of decision.	Static ataxia.	Body sway suggestibility.	Grip.	Word dislikes.	Personality inventory.	Life scale	Critical flicker fusion.	Autokinetic movement.	Autokinetic suggestibility.	Backward sway.	Fluency.
	V_1.	V_2.	V_3.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17
V_1	/	−·121	·002	−·147	·013	−·007	−·068	−·012	−·005	−·107	·068	−·021	·133	·225	−·292	−·084	·067	·020	−·055	·016
V_2	·121	/	−·394	·152	−·053	−·006	−·033	−·080	·014	·046	·025	−·278	·177	−·031	·051	−·163	−·058	·023	·214	·065
V_3	·002	−·394	/	·188	·073	·305	·008	−·337	−·025	·077	·025	·466	−·101	−·063	−·156	·131	−·032	−·034	·248	−·073
1	−·147	·152	·188	/	−·058	·130	·078	−·010	−·151	−·094	−·015	·075	−·065	−·144	−·277	·132	−·203	−·133	·354	−·181
2	·013	−·053	·073	−·058	/	·027	·123	−·115	−·107	·043	·018	·022	·081	·103	−·072	·010	·029	·095	−·014	·078
3	−·007	−·006	·305	·130	·027	/	−·033	−·075	·007	·022	·004	·290	−·234	−·127	−·029	·070	·007	−·395	·331	·136
4	−·068	−·033	·008	−·078	·123	−·033	/	·017	−·071	·033	−·015	·188	·040	−·088	−·072	−·050	·088	·177	−·126	−·143
5	−·012	−·080	−·337	−·010	−·115	−·075	·017	/	·072	−·015	·091	−·167	−·075	·189	−·006	·035	−·081	−·012	−·176	·045
6	−·005	·014	−·025	−·151	−·107	·007	·071	·072	/	·135	·035	−·076	·084	·099	−·034	−·113	−·080	·100	−·109	−·038
7	−·107	·046	·077	−·094	·043	·022	·033	−·015	·135	/	·621	−·028	·083	−·043	·104	−·190	·382	·047	·092	−·142
8	·068	·025	·025	−·015	·018	·004	−·015	·091	·035	·621	/	−·049	·054	−·010	·012	−·146	·130	·155	·035	−·067
9	−·021	−·278	·466	·075	·022	·290	·188	−·167	−·076	−·028	−·049	/	−·220	−·174	−·106	−·016	−·160	·048	·200	·032
10	·133	−·177	−·101	−·065	·081	−·234	·040	−·075	·084	·083	·054	−·220	/	·102	−·029	·023	·225	·089	−·081	·174
11	·225	−·031	−·063	−·144	·103	·127	·088	·189	·069	·043	−·010	−·174	·102	/	−·296	−·020	·027	·048	−·156	·091
12	−·292	·051	−·156	−·277	−·072	−·029	−·072	−·006	−·034	·104	·012	−·106	−·029	−·296	/	·092	·102	·030	−·014	−·192
13	−·084	−·163	·131	·132	·010	·070	−·050	·035	−·113	−·190	−·146	−·016	·023	−·020	−·092	/	·070	−·131	·002	·242
14	·067	−·058	−·032	−·203	·029	·007	·088	−·081	−·080	·382	·130	−·160	·225	·027	·102	·070	/	·045	·062	·047
15	·020	·023	−·034	−·133	·095	−·395	·177	−·012	·100	·047	·155	·048	·089	·048	·030	−·131	·045	/	−·042	−·149
16	−·055	·214	·248	·354	−·014	·331	−·126	·176	−·109	·092	·035	·200	−·081	−·156	−·014	·002	·062	·042	/	·110
17	·016	·065	−·073	·181	·078	·136	−·113	·045	−·038	−·142	−·067	·032	·174	·091	−·192	·242	·017	−·149	·120	/

TABLE III.

Test.	Centroid factor saturations. I.	II.	III.	Correlation with criterion.	Score multiplier for rotation.	Rotated factor saturations. I.	II.	III.
1. Intelligence	·520	·203	·149	—·053	— 1	—·010	·577	·028
2. Tapping area	—·038	·210	—·107	—·244	— 1	·156	·006	·181
3. ,, speed	·432	·129	·099	·088	1	·049	—·458	—·028
4. Level of aspiration	—·130	·190	—·360	—·056	— 1	·095	—·159	·385
5. Motor speed test	—·123	—·249	·245	·215	1	·071	·121	·343
6. Speed of decision	—·158	—·120	·111	—·172	— 1	·007	—·148	—·173
7. Static ataxia	—·467	·437	·258	—·304	— 1	·656	—·184	—·106
8. Body sway suggestibility	—·358	·355	·225	—·183	— 1	·529	—·126	—·097
9. Strength of grip	·326	·246	—·339	—·052	— 1	—·052	·271	·454
10. Word dislikes	—·250	·115	·131	—·237	— 1	·250	—·142	—·102
11. Personality inventory	—·157	—·094	·209	—·064	— 1	·061	—·108	—·249
12. Lie scale	—·121	—·091	—·160	—·008	— 1	—·076	—·188	·086
13. Flicker fusion	·245	·031	·113	..	..	..	..	..
14. Autokinetic movement	—·271	·346	·138	—·167	— 1	·454	—·079	—·011
15. Autokinetic suggestibility	—·394	·061	—·283	·045	1	—·129	·415	—·223
16. Backward "S"	·391	·393	·063	·065	1	—·176	—·502	—·168
17. Fluency	·250	·161	·334	·027	1	—·136	—·379	·191

ward movement exceeds the upward, then the score is down, score 2. If the line is less than $\frac{1}{2}$ in. *or* the upward movement exceeds the downward, the score is up, score 1.

(15) *Backward "S."*

The subject is required to draw S's in the ordinary position for 15 seconds, then backward S's for 15 seconds. The test score is the total number of backwards S's the subject is able to complete correctly.

(16) *Fluency.*

The subject is told to name as many round things as he can think of in one minute; the test score consists of the number of round things named by the subject.

(5) Results.

The intercorrelations between the 17 tests are reported in Table II for the 100 twins, as well as correlations with zygoticity, sex, and age. Table III records saturations of the tests for three significant factors, which leave only insignificant residuals. Also given in Table III are the correlations of each test with the criterion (these are bi-serial correlations; all others are product moment correlations). Item 13 has been omitted from further calculations, as it was impossible to give this test to the neurotic group. In order to rotate the factors so as to obtain maximum correlations with the criterion, those tests which showed negative correlations with the criterion were multiplied by -1, as indicated in Table III; this is merely a device which reverses the direction of scoring of the tests affected, and leaves the data unchanged in any material way. The last columns of Table III give the rotated factors. The new Factor I correlates ·758 with the criterion column, having been rotated into maximum agreement with it. Factor II was then rotated in such a manner as to preserve othogonality with Factor I, and to take up all the remaining variance on the intelligence test. Factor III is irrelevant to our purpose, and no interpretation of it will be attempted. Interpretations of Factors I and II are straightforward and dictated by the results: Factor I is a factor of neuroticism, Factor II one of intelligence.

Table IV gives the means and variances for the neurotic children, the identical twins, and the fraternal twins, on all 17 tests and also on the factor score for the "neuroticism" factor. The first three columns give the means for the three groups; only two of the differences between identical and fraternal twins are significant at the 5 per cent. and the 1 per cent. levels respectively, viz. the neurotic inventory and the lie scale. It is difficult to interpret these results, particularly in view of the fact that the inventory did not discriminate at all between normal and neurotic children. Why identical twins should be more given to lying than fraternal twins we cannot explain. The next three columns give the variances for all the children as individuals; the only difference, at the 2 per cent. level of significance, is on the Static Ataxia test, where identical twins are more variable than fraternal twins. (Only differences between the two types of twins are reported, as no particular interest attaches

TABLE IV.

Description of test.	Means.			Variances: Individuals.			Pairs.	
	Neurotics.	Identicals.	Fraternals.	Neurotics.	Identicals.	Fraternals.	Identicals.	Fraternals.
1. Intelligence	14·86	14·82	13·52	14·02	24·48	14·46	47·50	24·48
2. Tapping area	19·05	12·42	12·66	181·80	95·06	67·54	113·86	57·36
3. ,, ,, speed	43·33	45·34	45·22	71·62	65·33	71·56	102·90	91·13
4. Level of aspiration	32·86	31·74	29·84	151·38	144·64	255·69	192·26	277·70
5. Motor speed test	49·05	59·95	59·50	223·06	402·08	338·42	693·62	441·12
6. Speed of decision	3·94	3·02	3·00	7·54	2·54	4·33	3·43	3·80
7. Static ataxia	3·07	2·10	1·81	1·36	2·61	1·12	4·94	1·74
8. Body sway suggestibility	4·74	3·10	3·50	8·55	7·30	10·26	12·86	11·59
9. Strength of grip	68·57	68·74	68·32	85·46	98·40	107·49	185·26	159·33
10. Word dislikes	10·81	8·36	9·12	21·11	9·09	7·33	13·90	10·30
11. Personality inventory	12·86	10·70	13·14	35·10	34·38	22·74	47·42	29·10
12. Lie scale	1·33	1·66	0·96	1·43	1·58	1·10	2·36	1·29
13. Flicker fusion	*	2657·64	2613·64	*	71769·81	62204·32	124436·59	76820·54
14. Autokinetic movement	21·74	15·95	17·50	101·29	131·27	136·92	231·06	169·88
15. ,, suggestibility	1·43	1·48	1·50	0·26	0·26	0·26	0·40	0·29
16. Backward "S"	9·90	11·24	10·58	26·23	35·66	37·02	61·92	55·78
17. Fluency	10·05	10·28	10·40	16·69	18·66	11·63	25·50	13·04
18. Factor score (neuroticism)	*	23·20	22·96	*	91·55	41·47	172·67	50·83

* Test 13 could not be applied to the neurotic children. Factor scores were not calculated for neurotic children.

to differences between normals and neurotics, apart from the correlation of each test with this dichotomy, which is given in Table III).

The last two columns give variances for identical and fraternal twins taken as pairs. In 16 out of 18 cases the identical twin variance is larger; two of these differences are significant at the 2 per cent level (static ataxia and neuroticism factor Score). There seems to be little doubt that in our sample identical twins and fraternal twins have almost identical means with respect to neuroticism (23·20 and 22·96 respectively), but that the identical group contains pairs of twins tending to be more extremely unstable, and more extremely stable, than the fraternal twin group. We cannot explain this finding and must wait for a replication of the experiment before trying to generalize this tendency to all twins.

TABLE V.—*Raw Intraclass Correlations Between Twins, Correlations of Traits with Age and Resulting Partial Correlations.*

Trait.	Identical twins.			Fraternal twins.			Hereditary determination h^2.
	Between twins.	With age.	Partial.	Between twins.	With age.	Partial.	
1. Intelligence	·905	·208	·890	·670	·168	·660	·676
2. Tapping area	·193	·187	·164	−·148	−·068	−·144	·269
3. ,, speed	·557	·105	·552	·266	·508	·011	·547
4. Level of aspiration	·320	−·256	·272	·084	·218	·038	·243
5. Motor speed test	·700	−·399	·643	·296	−·265	·243	·528
6. Speed of decision	·340	−·046	·339	−·122	−·009	−·122	·193
7. Static ataxia	·857	−·066	·856	·537	·101	·532	·692
8. Body sway suggestibility	·737	·104	·734	·128	−·045	·110	·701
9. Strength of grip	·850	·580	·774	·468	·354	·392	·628
10. Word dislikes	·512	−·060	·510	·394	−·152	·380	·210
11. Personality inventory	·369	−·081	·365	·273	−·046	·257	·145
12. Lie scale	·485	−·090	·481	·167	−·254	·109	·418
13. Flicker fusion	·709	·110	·705	·229	·157	·209	·627
14. Autokinetic movement	·734	−·210	·722	·228	·151	·210	·648
15. ,, suggestibility	·534	·011	·534	·141	−·081	·135	·461
16. Backward "S"	·711	·333	·708	·491	·161	·477	·423
17. Fluency	·357	−·077	·353	·118	−·068	·114	·270
Neuroticism" factor	·851			·217			·810

Table V shows the raw intraclass correlations between twins of both types, correlations with age, and the partial correlations resulting from eliminating age differences. It will be seen that age plays little part in determining scores, and that correction leaves the correlations very much as they were before. The last column of Table V gives Holzinger's h^2 values, i.e. the extent to which each test variance is determined by heredity. It will be seen that the test of intelligence has an h^2 (·676) which is almost identical with the h^2 values given by the best neuroticism tests: Static ataxia (·692), autokinetic movement (·648) and suggestibility (·701).

As the last step in this procedure, factor scores on the neuroticism factor were calculated for each twin and h^2 values calculated for these "neuroticism scores."

$$h^2 = \frac{i^r - f^r}{1 - f^r} = \frac{(1 - f^r) - (1 - i^r)}{(1 - f^r)}$$

where $_{i}r$ = intraclass correlation for identical twins and $_{f}r$ = intraclass correlation for fraternal twins, it follows that

$$(1 - {}_{i}r) = \frac{\text{"within"}_{i}\text{ variance}}{\text{"total"}_{i}\text{ variance}} = \frac{13{\cdot}680}{91{\cdot}551} = 0{\cdot}149, \text{ from which } {}_{i}r = {\cdot}851.$$

Similarly, $(1 - {}_{f}r) = \frac{\text{"within"}_{f}\text{ variance}}{\text{"total"}_{f}\text{ variance}} = \frac{32{\cdot}480}{41{\cdot}468} = 0{\cdot}783$, from which $_{f}r$ = ·217. It follows that $h^2 = 0{\cdot}810$. This value is considerably higher than that given by any single test, and indicates that the factor constitutes a biological unit which is inherited as a whole.

The h^2 technique used in this paper gives the per cent. of twin difference variance attributable to nature providing that certain assumptions are met. Two of these assumptions are that nurture influences are the same for both types of twins, and that differences due to nature are uncorrelated with differences due to nurture. It is probable that these assumptions are not completely met, and that consequently our estimate is too high. On the other hand, another assumption, viz, that the variance due to errors of measurement is negligible, is quite certainly not fulfilled, and in view of the known unreliability of personality tests we must assume that errors of measurement may play a considerable part. This would lead one to believe that the found h^2 would be an underestimate of the true value, and it seems not impossible that this factor may cancel out the two previously mentioned. It is possible, therefore, to argue that the h^2 found is a rough and ready estimate of the contribution which heredity makes to individual differences in neuroticism.*

Our conclusion regarding the rise of this contribution is not in agreement with that arrived at by Newman, Freeman and Holzinger (1937). They find that "the only group of traits in which identical twins are not much more alike consists of those commonly classed under the heading of personality . . . ," we have shown that identical twins show a correlation on neuroticism of ·851, while fraternal twins show a correlation of only ·217. From this it was concluded that individual differences with respect to neuroticism, stability, integration, or whatever we may wish to call this trait or factor, are determined to a very marked extent by heredity, and very much less markedly by environment. This conclusion, of course, applies only in the general type of environment from which all our twins came, and might not be applicable under conditions of more extreme environmental variation, such as may obtain in other cultures.

(6) Summary and Conclusion.

Twenty-five pairs of identical and 25 pairs of fraternal twins were tested with a battery of objective personality tests. A group of 21 neurotic children equal in age to the twins, were also tested and constitute a criterion group. The tests used were intercorrelated for the total twin population tested, and a

* We have used Holzinger's h^2 statistic in our estimates because no better estimate of the contribution of heredity to the total variance is available. In view of the various assumptions involved in this statistic we do not feel too much confidence in the accuracy, and would lay more stress on the directly observed intraclass correlations for identical and fraternal twins. A note by Joan May, from the Statistical Section of the Psychology Department, is appended to show more precisely the assumptions involved in Holzinger's argument.

factorial analysis carried out, using the method of "criterion analysis." In addition to other factors, a "neuroticism" factor was extracted. Factor scores were calculated for this factor, and intraclass correlations derived for the identical and fraternal twins. These correlations have the values of ·851 and ·217 respectively, giving rise to an h^2 value of ·810. If we can interpret this value, as Holzinger does, as measuring the contribution of heredity to the total variance, it would follow that some 80 per cent. of individual differences in the neuroticism factor were due to heredity and only about 20 per cent. to environment. In view of the many assumptions underlying the derivation of h^2 this interpretation is put forward with great hesitation. Regardless of the particular interpretation made of h^2, however, it has been shown that the factor of neuroticism is not a statistical artefact, but constitutes a biological unit which is inherited as a whole. From the methodological point of view this latter conclusion is perhaps as important as a demonstration that neurotic predisposition is to a large extent hereditarily determined.

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NOTE ON THE ASSUMPTIONS UNDERLYING HOLZINGER'S h^2 STATISTIC.

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Holzinger set up his equations to show the combination of the factors —nature (A), nurture (B), and error(E)—which go to make up a score obtained by a particular twin on a particular test. If ${}_iX_1$ and ${}_iX_2$ are the twins in an identical pair and ${}_fX_1$ and ${}_fX_2$ are the twins in a fraternal pair then :—

$$(1)\ \begin{cases} {}_iX_1 = {}_iA + {}_iB_1 + {}_iE_1 \\ {}_iX_2 = {}_iA + {}_iB_2 + {}_iE_2 \end{cases} \qquad ({}_iA_1 = {}_iA_2 = {}_iA)$$

$$(2)\ \begin{cases} {}_fX_1 = {}_fA_1 + {}_fB_1 + {}_fE_1 \\ {}_fX_2 = {}_fA_2 + {}_fB_2 + {}_fE_2 \end{cases} \qquad (\textit{note } {}_fA_1 \neq {}_fA_2).$$

It should be noted here that no provision has been made for an interaction term between factors A and B. It is certain that such interaction takes place, and that a term of this kind should be included in a complete account.

Holzinger then considers the difference within a pair of twins—both identical and fraternal. Using his notation we have the difference between a pair of identical twins ${}_iD$, where—

$$\begin{aligned} {}_iD &= {}_iX_1 - {}_iX_2 \\ &= {}_iD_B + {}_iD_E. \end{aligned}$$

The variance of this difference (${}_i\sigma^2{}_D$) will be—

$$\begin{aligned} {}_i\sigma^2{}_D &= {}_i\sigma^2{}_B - r_{B_1B_2}\,{}_i\sigma^2{}_B + {}_i\sigma^2{}_E{}^* \\ &= {}_i\sigma^2{}_{D_B} + {}_i\sigma^2{}_E. \end{aligned}$$

It will be seen that Holzinger gives (p. 113 [15])

$$ {}_i\sigma^2{}_D = {}_i\sigma^2{}_{D_B}.$$

assuming that—

(1) ${}_i\sigma^2{}_E = 0$
(2) $r_{EB} = 0$.

Considering these assumptions,

(1) The error variance cannot be equated to zero. It is obvious that one cannot eliminate experimental error—its inclusion in an equation of the above type (1) is fundamental.

* Since ${}_i\sigma_{B_1} = {}_i\sigma_{B_2} = {}_i\sigma_B$. It should be remembered that in Holzinger's notation ${}_i\sigma_B$ is a double entry standard deviation of the difference ${}_iD_B$.

(2) By definition of our error term we can assume orthogonality of any residual.

Similarly Holzinger considers the difference ($_fD$) between a pair of fraternal twins where—

$$\begin{aligned} {}_fD &= {}_fX_1 - {}_fX_2 \\ &= {}_fD_A + {}_fD_B + {}_fD_E \end{aligned}$$

as over, the variance of this difference ($_f\sigma^2{}_D$) will be—

$$_f\sigma^2{}_D = {}_f\sigma^2{}_A - r_{A_1A_2}{}_f\sigma^2{}_A + {}_f\sigma^2{}_B - r_{B_1B_2}{}_f\sigma^2{}_B + 2R\sigma_{D_A}\sigma_{D_B} + {}_f\sigma^2{}_E.$$

Therefore $_f\sigma^2{}_D = {}_f\sigma^2{}_{D_A} + {}_f\sigma^2{}_{D_B} + 2R\,{}_f\sigma_{D_A}\,{}_f\sigma_{D_B} + {}_f\sigma^2{}_E$, where R = correlation between D_A and D_B.

Holzinger gives the variance of the difference

$$\sigma^2{}_D = {}_f\sigma^2{}_{D_A} + {}_f\sigma^2{}_{D_B} + 2R\,{}_f\sigma_A\,{}_f\sigma_B \qquad \text{(p. 113 [16])};$$

and on p. 114 assumes $R = 0$, i.e. :

$$_f\sigma^2{}_D = {}_f\sigma^2{}_{D_A} + {}_f\sigma^2{}_{D_B}$$

assuming that—

(1) $_f\sigma^2{}_E = 0$
(2) $r_{EA} = r_{EB} = 0$.
(3) $R = 0$.

Again, in considering these assumptions,

(1) The error variance is not zero.

(2) It is legitimate to assume that $r_{EA} = r_{EB} = 0$.

(3) This will be true if $r_{AB} = 0$, which Holzinger has implicitly assumed. It is certain, however, that there is a correlation between the nature and nurture factors.*

Unless we make definite assumptions about—

(1) The size of R,

(2) The relative sizes of the two error variances,

it can be seen from (17), p. 113, and (25), p. 115, that it cannot be shown whether the more accurate estimates of the variances of the differences will increase or decrease h^2.

* Shuttleworth *J. ed. Psychol.*, **26**, Part 1, 561–578, "The Nature *versus* Nurture Problem." Part 2, 655–681.

INTELLIGENCE AND MODERN SOCIAL TRENDS.*

By E. O. Lewis, D.Sc., M.R.C.S.

Mental deficiency and its synonym "oligophrenia" are terms interpreted very differently in various countries; this has made it almost impossible to compare the statistical data of these countries. The concept the lay person in this country has of mental defect applies with few exceptions to individuals with intelligence quotients below 60 per cent., i.e., idiots, imbecile and obvious simpletons. When a person with this conception of mental defect—and we must admit that it corresponds fairly closely to the legal interpretation of the Mental Deficiency Acts in this country—is told that mental deficiency is a major social problem, the statement is received with some measure of incredulity. There is some justification for this incredulity. The statement is ambiguous and is based upon some rather muddled thinking. If we accept this legal and administrative interpretation of mental defect only about 1 per cent. of the population can be said to be mentally defective. Probably no other 1 per cent. of the population has such a high proportion of decent, docile and law-abiding citizens. If so, what meaning can we give to the statement that mental deficiency is a major social problem?

In this paper it is not proposed to discuss mental deficiency in the somewhat narrow, legal and administrative sense, but I should regret very much if anything I say or do not say were interpreted as indicating an indifference to, or any complacency about, the administration of the Mental Deficiency Acts. We are very far from fulfilling our duty as a nation to the mentally defective. For example, the Mental Deficiency Departmental Committee estimated, about twenty years ago, that institutional accommodation was required for 110,000 mental defectives. The Acts have now been in force 35 years, and the total number in Institutions to-day is only 55,000. The care and supervision of defectives remaining in the general community is in an even worse state; many local authorities have made scarcely any such provision.

Moreover, the importance of the study of mental deficiency as a branch of medical science needs to be emphasized. The thousands of lower grade defectives in our large institutions, as well as those in the general community, present one of the most fertile fields for medical research. The science and art of endocrinology had its origin in the study of cretinism. Doubtless there are other sciences and arts waiting to be discovered by the intensive study of these experimental failures of Nature—the lower-grade defectives.

Whilst mental deficiency, when interpreted in the narrow legal sense, may not be said to be a major social problem, those of us, who have to deal with the higher grade defectives in the general community, are firmly con-

* Presidential address given to the Section of Psychiatry of The Royal Society of Medicine on 10 October, 1950.

vinced that we are brought into contact with a section of the community that *does* present very serious social problems. The phrase "major social problem" may not apply to persons with I.Qs. below 60 per cent. but certainly does to the much larger section of the community with I.Qs. from 60 per cent to 85 per cent. Only a relatively small proportion of the latter group can be brought within the scope of the Mental Deficiency Acts. In this paper it is proposed to discuss the problem of this larger group of persons, whose basic handicap is their poor mental endowment.

Numerous surveys have been made to determine the distribution of intelligence amongst the general population. The data of the majority of the surveys indicate that from 8 to 15 per cent. of the community have I.Qs. below 85 per cent. When we think of the innumerable surveys made in various countries, it can be stated with some degree of certainty, that in the whole field of psychiatry there are few facts so well established statistically as this one.

The interpretation of results obtained by the application of intelligence tests is a very controversial subject. Recently some psychologists have urged that the concept of general intelligence needs overhauling, and some have even advocated that it should be abolished. Whilst the academic psychologists decide this issue, I am prepared to accept as a working hypothesis Burt's concept of intelligence—that of an innate general ability largely inherited.

Environmental factors, especially scholastic attainments, determine in some measure an individual's score with intelligence tests. Researches dealing with this special point indicate that 20 to 25 per cent. of the score may be attributed to these factors. From considerable experience in the application of these tests to large numbers of school children, some in rural districts, others in small urban areas and many in large towns, coming from homes that differ greatly in their economic, cultural and social status, I think this estimate is about right, although in exceptional cases, adverse environmental factors may lower the score to an even greater extent.

After making allowances for these and other factors that influence scores in intelligence tests, it seems to me that a conservative estimate of the proportion of the population with 60 per cent. to 85 per cent. of normal intelligence would be 5 per cent. Various names have been given to this group of the community. On the Continent, the term "oligophrenia" comprises not only this group, but the lower grade mental defectives. American psychologists refer to the members of this group as "morons." In this country the terms backward, dull and retarded are preferred, but are applied with considerable laxity. Some years ago, I ventured to suggest that the term "subcultural" should be used to designate this group, but I am not much enamoured of this term, and would gladly accept a more suitable one. The term "subcultural" may serve our purpose until some popular journalist debases it to an epithet of abuse.

Of the 5 per cent. of the population that constitutes the subcultural group only about $\frac{1}{2}$ per cent. can be brought within the jurisdiction of the Mental Deficiency Acts. There is little prospect of a wider or more liberal interpretation of mental defect being adopted in this country—even if this were desirable. The lay public should be got to realize that for every one person that can be

dealt with under these Acts, there are five or more borderline cases who are social failures, actually or potentially, and that their failure is primarily due to poor mental endowments. This marginal group requires much more consideration than it has received hitherto, because it is the members of this group, in my opinion, who present serious social problems.

The following are some of the features of the subcultural group that make it of special interest.

The numbers of any community comprised in the subcultural group may be said to be an index of the general level of intelligence of the whole community. This cannot be said of lower grade defectives—idiots and imbeciles. The large majority of these are due to pathological factors, or if the condition is inherited, to genes that are comparatively rare. It is possible to conceive a substantial increase in the numbers of lower grade defectives without any appreciable modification of the average level of intelligence of the general community. Any material change in the numbers of the subcultural group will modify the form of the curve representing the distribution of intelligence in the whole community. This subcultural group is an integral part of the general population. If this view is accepted, it follows that the numbers in this group must be some index of the level of intelligence in the whole community or nation.

During the last two decades there has been much controversy whether the average level of intelligence in this country has been falling. It seems to me that the real practical point at issue has been whether there has been a substantial increase in the numbers of persons that can be included in the category of the subcultural. Those who have maintained that the level of national intelligence is falling, have based their case chiefly upon the differential fertility of the various economic and social classes. Children with lower intelligence generally belong to larger families, and the more intelligent children are to be found in the smaller families. The fathers of large families are mostly unskilled workers, whilst small families are to be found amongst the professional classes and skilled artisans. On *a priori* grounds this differential fertility must result, if continued for a number of generations, in an increase in the numbers of the subcultural group and in the lowering of the average intelligence of the community, provided there are no compensating factors to raise the average level of intelligence.

Psychometricians have tried to obtain direct evidence of these changes. The Scottish Council for Research in Education carried out surveys for this purpose. All children aged 11 in the schools were given group tests. The first survey was made in 1932 and the second in 1947. In the first survey the average score was 34·5 points out of a maximum of 76 ; in the second survey the average score was 36·7 points—a significant increase of 2·2.

The average intelligence of American soldiers who participated in World War II was found to be definitely higher than those who participated in World War I. The data obtained by de Grout, on the other hand, who tested 13-year-old children, indicated that the post-war group scored on an average 4 points less than the pre-war group.

The Scottish Council have been cautious in their interpretation of the

improvement in the average score. The Council recognizes that an increasing familiarity with mental tests—" test sophistication " as it has been called—may have enabled the children to improve their score. Special studies made by psychologists to assess the effects of practice show beyond any doubt that the improvement due to practice alone may be considerable. It would be contrary to all we know about the foresight of our friends born and bred North of the Tweed, to assume that Scottish teachers, during the fifteen years that intervened between these two surveys, refrained from giving their pupils some drill in mental tests, especially when the teachers knew that these tests were being used in the selection of pupils for post-primary schools. Amongst other factors that may account for the increase in the scores is the acknowledged improvement in physical fitness, more especially in the nutritional condition of school children during the last two decades. Whilst the pessimism based upon differential fertility of the social classes receives no support from the Scottish surveys, I do not think the results do much to allay our apprehension.

Penrose has written recently that " defectives are the genetical backbone of the population." His remark does not engender much optimism about the future of the human race, but both Penrose and Haldane have given a timely corrective to the pessimism that is based solely upon the differential fertility. In the fields of medicine and biology there have been, from time to time, false alarms because important factors that tend to restore and maintain a state of biological equilibrium have been ignored. Genetic safeguards must have been operative throughout the centuries to have enabled the human race to attain its present level of mental development, in spite of its many vicissitudes. Research is much needed to elucidate these safeguards. Penrose and Haldane have intimated what they believe to be some of the safeguards, namely, assortative mating, the sterility of lower grade defectives and the higher infantile mortality in the poorer stratum of the population. In addition it seems to me that the whole bias for the transmission of normal characteristics, as exemplified by what geneticists term " the regression to the mean," makes for stability. For instance, if both parents have I.Qs. of 80 per cent. the average I.Qs. of the children will probably be half way between this and the normal, that is, their average I.Qs. will approximate to 90 per cent.

Belief in the biological stability of the race does not justify indifference to dysgenic tendencies, such as the differential fertility of intelligent and unintelligent persons. No amount of theorising can discount what has been observed to take place in certain small communities in this country and others during the last hundred years. The biological equilibrium has been seriously upset in certain small rural communities where there has been inbreeding of poor mental stock. Dr. Répond, at a recent meeting of the Royal Medico-Psychological Association, gave a vivid account of such a community in a remote Swiss valley ; the community had deteriorated to such an extent that 27 per cent. of the school children were mentally defective. In the course of my surveys for the Departmental Committee I found many " pockets " in rural areas from which there had been rapid migration during the last fifty years, leaving a residual population of poor mentality. In these areas the incidence of subnormal intelligence was considerably higher than the average.

Earlier in this paper I expressed the opinion that if mental deficiency is interpreted in the legal sense, the mentally defective cannot be said to present a serious social problem, but the much larger borderline group, the subcultural, certainly does. It is dangerous to attempt prophesy in any field of science, but probably in the new science of Social Medicine the subcultural section of the community will occupy a prominent place. The study of mental deficiency, using this term in the narrow sense, can rightly claim to have made some valuable contributions to clinical medicine. Those who have worked in this field can claim to have drawn attention to a much larger problem, that of the subcultural, which up to the present can be aptly described as " no man's land " in the field of psychiatry.

Our reaction to any new problem may be any one of the following: We may adopt the attitude that there is no real problem; this is the easiest way of disposing of any problem. Or we may recognize that there is a problem, but dismiss it as one of little importance—this is the next easiest solution. Or again, we may admit that the problem exists and that it is indeed important, but as there is no obvious solution why trouble about it? This is the commonest attitude. The fourth attitude is to recognize the importance of the problem, and to settle down to study it and discover some practical solution; this is too often a rare response.

Those who refuse to recognize that the subcultural group presents a problem when confronted with a person who belongs to this group, reason somewhat as follows: The person is either mentally defective or not. If he is a defective, he can be dealt with under the Mental Deficiency Acts; if not, he must be treated as a normal person. For people who reason thus everything is either black or white; for them there are no greys. This kind of intellectual colour-blindness is rather prevalent amongst members of the legal profession and certainly not absent from our own.

We are rightly proud as a nation that our judges and magistrates guard jealously the rights and freedom of the individual. At the same time, those of us who have been intimately associated with the administration of the Mental Deficiency Acts, could give many instances when the judicial authority has either refused to make an Order under these Acts, or has pressed for the discharge of a patient from an Order, with the result that it has left on the hands of the administrator, not only an unsolved problem, but one aggravated. Such action has often been a dis-service to the individual involved and detrimental to the community in which he lives.

The purist in dichotomy in our own profession concerns us more intimately. We frequently read in case studies that the patient was not mentally defective, but simply dull and backward; but this feature of the diagnosis receives no further attention, as if it were of no importance. Whatever the predominant feature of a case may be—psychosis, neurosis or anti-social behaviour—that the patient should be a person of poor mental endowments is a matter of considerable importance, not only in the diagnosis, but also in the treatment and subsequent rehabilitation of the patient.

The second attitude, namely, that of recognizing that the subcultural group presents a problem, but of regarding it as of no importance, has many

forms of expression. Some who adopt this attitude dismiss the subject by saying " there have always been and always will be hewers of wood and drawers of water "—thus showing a nodding acquaintance with the Scriptures. Others express the attitude by attempting to discredit the mental tests which have been instrumental in differentiating the subcultural from the normal. These tests, it is maintained, are scholastic in character, and such knowledge is of little importance when we come to the practical problems of living. We are told that general and compulsory education is a comparatively recent feature or fad of Western civilization. We are reminded that England forged ahead to become the foremost nation in industry and world politics when more than half the population was illiterate.

With all its defects it can be claimed that the school of to-day has proved itself to be a reliable testing ground of innate mental ability, and gives a fairly reliable forecast of the relative efficiency of the children as future citizens. Retarded children leave school greatly handicapped and very poorly equipped to fend for themselves in a competitive world. A serious indictment of our educational system—and in saying this I hope I am not using words thoughtlessly—is, that these retarded children leave school worse equipped than they need be. One of the most disturbing discoveries of my examination of thousands of school children was that the " educational " retardation on an average is double that of the " mental " retardation. That is, if a child of 12 had a mental age of 10, his educational attainments were only those of a child of 8. The neglect of the retarded child means that large numbers leave our schools with feelings of inferiority and frustration deeply imbedded. What fertile soil for neurosis, and even psychosis, not to mention anti-social behaviour ! That at least two million of the forty odd million population of England and Wales can be said to belong to the category of the subcultural, surely makes this section and the problems it presents of great social importance. From the standpoint of Social Medicine, this is the most important psychiatric group in the whole community.

The third attitude mentioned is that of recognizing that the problem exists, and that it is an important one, but against that as no solution seems possible, no good purpose would be served by discussion. This attitude of futility seems to be the most common one, even amongst the more intelligent section of the community. The best way of discounting this attitude is to proceed to discuss the fourth attitude mentioned, namely, that which attempts to study the nature of the problem and to determine what can be done about it.

The right approach to the subcultural section of the community, as already indicated, is that of regarding it as an integral part of the general community. The problem presented by large numbers of the lower grade defectives and many of the feebleminded who can be brought within the scope of the Mental Deficiency Acts, can only be solved by their segregation, temporarily or permanently, in institutions or colonies. When dealing with the subcultural group the solution cannot be one of segregation, but must be that of assimilation into the general community. Whilst emphasizing the antithesis between the mentally defective and the subcultural it is obvious that there is some overlapping

of these two groups. Many of the feebleminded are of the subcultural type, and numbers of these, after a period of segregation for training and stabilization, can return and become useful members of the general community. This overlapping does not invalidate our main thesis, namely, that the problem the subcultural group sets us is one of assimilation and not of segregation.

The recent Education Acts (1944) recognize that retarded children, the young generation of the subcultural, must remain an integral part of the general school population. It is gratifying that our legislators realize that this is the right line of approach. Let us hope, however, that the errors of the past will be avoided. In the education of the retarded, emphasis should be placed, not on the scholastic, but on the social aspect. Our educational system has one serious failing—its detachment from the home. The problem of the subcultural is largely a family problem. If the children of this group are to become good and useful citizens there must be co-operation between the home and the school; and to ensure such co-operation the Education Authority must take the initiative. Teachers and parents should not be strangers to one another. To ensure continuous co-operation between the home and school, the services of social workers are essential. Those who have experience of Child Guidance clinics will probably agree that in many cases the crux of the problem is in the home and not in the child.

From the standpoint of Social Medicine the subcultural group presents larger and more difficult problems than the mentally defective. The majority of our chronic social problems—pauperism, slumdom and recidivism—are associated, not so much with the 300,000 mental defectives in the country, but with the two million borderline group. In a paper published recently I endeavoured to indicate some of these problems. Social Medicine, still in its infancy, is chiefly concerned with environmental factors—bad housing, unhygienic conditions in factories and mines, and many other such factors that can be remedied, and much progress has already been made with many of these problems. Sooner or later with such problems a hard core is reached which cannot be resolved by methods hitherto successful. It is when Social Medicine has to deal with these residual hard cores that it will turn to the psychiatrist, because it will be realized that further progress cannot be made without taking into consideration the special features of the persons who constitute this hard core. To illustrate this I cited the statistics from infantile mortality in this country. In 1900 the infantile mortality for England and Wales was 153 per 1000 live births. By 1940 this rate had fallen to 50. During the last ten years there has been but little change in this rate. It seems that we are getting near the "hard core," which is by no means negligible. The nature of the residual problem is better understood when we analyse the infantile mortality rate for various social groups. Statistics show clearly that the greatest reduction in infantile mortality has occurred amongst the more intelligent and better educated; the least reduction is amongst the families of unskilled workers. The wives of professional and business men, technicians and skilled artisans have benefited greatly from the medical knowledge relating to pregnancy and childbirth that has been made available in books and articles written for the lay public and from the facilities provided in ante-natal clinics.

Mothers of poor intelligence have not profited to nearly the same extent ; the propaganda does not seem to have reached these mothers, and although they may have attended ante-natal clinics they have not been able to co-operate effectively with the doctors and nurses. Some new method of approach to this section of the community will have to be found before any further substantial reduction can be made in the infantile mortality of this country.

Many of the Social Services have developed considerably during the last few decades. The success and future development of these services will depend largely upon how the public use them. Recent experiences with the National Health Service give rise to some misgivings. The ingenuity shown in some of the abuses exonerates the members of the subcultural group. There is, however, the danger that certain members of this group may make an unduly large demand upon the National Health and other social services. If this occurs the benefit of the services to the whole community will be restricted and their development retarded.

This brings us to the controversial subject of the Social Problem Group. The central feature of this concept is that a relatively small proportion of the population makes an unduly large demand upon the various services. The smaller the group, the more significant becomes the concept. Recent surveys made in several of our large towns may give us, at an early date, an approximate idea of the size of this group. It would not be surprising to find that it is a small one, even a small minority of the subcultural group. The smaller the group the easier it should be to take practical steps to prevent it becoming a menace to our social services. When I have talked with general practitioners in rural and small provincial towns, or with Health Visitors who work amongst urban populations and have a thorough knowledge of certain areas, they have had no difficulty in understanding the concept of the Social Problem Group and have been able to give the names of several families who can be included in this group.

During the last century our country has experienced changes in its industrial and social organization, that may be said to be phenomenal in their rapidity, in the whole history of civilization. A century ago the population of this country lived mostly in rural areas and was occupied chiefly in agriculture. To-day the population is predominantly urban ; almost half of the total population is concentrated in a dozen large towns or dense urban areas. The majority of the men are occupied in large engineering works, mines, factories or offices. It is a tribute to the adaptability of the British character that this rapid urbanization and industrialization has been effected with so little social upheaval. Such changes, however, must have affected profoundly the mental habits and outlook of our nation ; but it is only of recent years psychiatrists have given much attention to these changes.

Mumford, in his volume on *The Culture of Cities*, has given us a comprehensive survey of the process of urbanization throughout the Western world. His almost wholesale condemnation of urbanization gave me the feeling that literary hyperbolism had been let loose in scientific fields. Possibly Mumford has exaggerated the disadvantages of urbanization and undervalued its gains, but he has focused attention upon several issues that are vital to the study

of modern Sociology. Here it is only possible to mention one or two issues that are most relevant to the problems presented by the subcultural group.

From the purely economic standpoint urbanization has probably improved the lot of those with poor intelligence. In every factory there are several mechanical and simple processes that such persons can perform. Group or teamwork that requires little initiative does not expose their limitations. Agriculture, on the other hand, now that it has become more scientific and mechanized, makes relatively less demand for unskilled labour. Therefore it seems that urbanization has rendered it easier to assimilate the subcultural group into the economic system of our country.

From a genetic standpoint also urbanization has certain obvious advantages. One of these is that eventually it will reduce the amount of inbreeding amongst families of poor stocks, physically and mentally. I have qualified this remark by saying "eventually," because it seems that during the last two or three generations the rapid process of urbanization has indirectly caused an increase in the incidence of mental deficiency in more rural areas, by leaving in these areas a residual population of poor mental endowments.

There appears to be no evidence that urbanization has been associated with any increase in the incidence of mental deficiency. The changes urbanization is actually producing in the mental endowments and in the functioning of these endowments should prove a fertile field for research. By applying group tests to large numbers of children in rural and urban areas I obtained a little information on this point. The difference between the average scores of children in urban and rural areas was so small as to be of no significance. In the rural areas there was more scattering of the scores, that is, a larger proportion of the scores were found at the extremes, both subnormal and supernormal, than in urban areas. This suggests that urbanization tends to standardize mental endowments and their functioning. The rural protagonist will probably express this more tersely by saying that in our large towns we are producng a population of standardized mediocrities.

The great contrasting feature between the social life in villages and small towns, on the one hand, and that in large towns, is in the degree of cohesiveness. In rural districts family bonds are stronger and the people know one another more intimately, and are interested in one another's affairs. Contrast this with the social life in our large towns. The attitude of the Londoner to the vast majority of people he meets each day can be appropriately described as mildly paranoidal. Neighbourliness is a lost and forgotten art in our large towns. People live thirty or more years in the same place without taking the slightest interest in local affairs or administration. In many of the dormitory suburbs there is practically no community life. If one may be allowed to indulge in paradox and hyperbolism, the population of a dormitory suburb can be described as an amorphous agglomoration of unsociables.

The massing of population in large towns of half a million to ten million inhabitants gives rise to innumerable sociological problems. The science of Social Psychology, although still in its infancy, has made some interesting contributions and is gradually elucidating some of the chief features of the

complex social organizations of our large towns. In this paper only one or two of these features can be mentioned.

Sociologists and social psychologists agree that in the large urban populations there is setting in a process of stratification. This tendency results in a grouping very different from that known as the social classes of the past and can be said to be superseding the class system. The concept of " social class " implies a subjective feeling of group interest and group membership. Stratification, on the other hand, is something objective and is determined in the earlier stages, at any rate, by factors chiefly economical or educational. Stratification is not merely a classification into the " haves " and " have-nots," especially in times when many artisans and even unskilled workmen earn better wages than the members of the " black-coated " fraternity. Some sociologists have maintained that the stratification in the large towns of some countries has gone so far as to produce a bi-polarized community. In such communities the large majority of people belong to one or other of two antagonistic groups whose viewpoints are basically irreconcilable. Their attitude to economic, cultural and moral issues, are completely opposed.

To return to our main theme, that of the assimilation of the cultural group into the life of the general community, it is obvious that this trend to stratification in our large towns renders the task of assimilation much more difficult. The great danger is that the subcultural group may be precipitated out of the general life of the community and form a lower stratum that will present many difficult social problems.

In rural districts and small towns in the past this assimilation has been effected without much difficulty or conscious effort. I may be allowed to illustrate this by a personal reference. I spent my youth in a small community in the Rhondda Valley of about 10,000 population. It was a community in which everyone depended for his livelihood, directly or indirectly, upon coal-mining. In this relatively small community there were few or no class distinctions. Owing to the perils of coal-mining the managers and the miners themselves were careful not to allow any person of poor intelligence or anyone whose behaviour was erratic to work down the mine. The simpletons and oddities were given work on the surface, and there was no dearth of suitable jobs for these people. If a person of apparently normal intelligence said that he worked on the surface of the mine he received what we know as the " interrogating look." The surface workers, although receiving lower wages than the miners, felt that they were an essential part of the industrial machine. The social life was largely associated with the Churches ; over 90 per cent. were church members. Possibly the cultural interests were narrow and occasionally trivial sectarian differences produced friction and excitement ; but it was a closely knit community. Serious crime was almost unknown and there was no slum area. although naturally homes differed somewhat in standards of cleanliness and hygiene. The weaker members of the community, of which there was at least the average number, were surrounded by friends and fellow workers, who gave them assistance and guidance when illhealth or misfortune threatened their homes. Far be it from me to suggest that the Rhondda was a Utopia in those days. The infantile mortality rate was the highest in the

country and large numbers of miners died in middle-age from a disease that we know now to be a combination of phthisis and pneumokoniosis, but it was a community with a high degree of cohesiveness, and for this reason, the subcultural group presented no serious social problem. Unfortunately, by to-day, much of this cohesiveness has been lost.

The decline in the social activities and interests of large numbers of those who live in our big towns or cities is a matter of some importance to the psychiatrist, who deals mostly with cases of psychosis or neurosis in the treatment of his patients. The goal of mental therapy is to produce a well integrated and fully developed personality. Even the best and most harmonious home environment cannot, of itself, produce this complete personality. Social activities outside the home are essential. We all know of instances of neurosis that can be attributed partly, if not wholly, to emotional stress or conflict in the home. In many of these cases, the patient would probably have been able to cope with the home situation had he cultivated social activities outside the home. This seems to me to be a problem that relates particularly to patients who have reached middle-age ; young people usually have plenty of social interests at their various clubs. The emphasis placed upon group activities, especially amongst convalescing patients, in our mental hospitals is an encouraging sign. There are many cases who fail to become properly rehabilitated when they return to the general community because there are few facilities in many of our large towns for social life outside the home.

Social Psychiatry is chiefly concerned with the mental health of the community as a whole, and it is from this standpoint we see the larger issues and wider problems presented by the social disintegration which is taking place in our large towns and cities. The seriousness of this problem is realized by many workers in various branches of social welfare, but it is too wide a subject for us to discuss fully in this paper. Unfortunately, the mass entertainments of the radio, television and cinema tend to aggravate this disintegration The crowd is the antithesis of the social group—that is, of the small group of people who meet to discuss their problems, and even if they do not reach agreement, endeavour to understand one another's standpoint and to agree upon some practical line of action.

This lack of cohesiveness in our large towns gives rise to many important problems which are outside the theme of this paper. Sociologists who study the broader issues of this subject would probably regard the assimilation of the subcultural group as one of the minor problems. Would it be any exaggeration to say that democracy has no greater or more urgent problem than that of ensuring a greater degree of social cohesion amongst the populations of large towns ? If the democratic countries fail in this task there is the danger that some kind of cohesiveness will be enforced by some arbitrary authority.

Owing to its discursive character this paper is not easily summarized. The problem presented by the subcultural group has been discussed in the light of a few modern social trends. The first trend discussed was that of the differential fertility of the various social groups. Whilst there is as yet no definite evidence to justify the pessimism of some geneticists and psychologists, several surveys made in recent years indicate that there is no ground for complacency.

Another trend considered was the rapid development of the social services. It is suggested that the unduly large demands the " social problem group " is likely to make upon these services will hamper their development. The other important trend discussed was that of urbanization. The social life in large towns lacks the cohesiveness found in rural and small urban districts. The chief problem the subcultural group presents is its assimilation into the social and economic life of the general community. This task is rendered much more difficult by the disintegration of social life that is taking place in large towns.

THE SURGICAL UNCERTAINTIES OF PREFRONTAL TOPECTOMY AND LEUCOTOMY (OBSERVATIONS ON 100 CASES).

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There is no branch of neuro-surgery in which the assessment of results is more difficult than in psycho-surgery. The main sources of uncertainty are :

(*a*) Mental impairment or improvement cannot yet be measured as precisely as neurological disorders, such as visual field or motor defects.

(*b*) Spontaneous recovery and the influence of the incidental psychotherapy and drugs involved in any form of surgical attention cannot be evaluated with certainty in many cases.

(*c*) Most of the cytoarchitectural fields of the frontal cortex cannot yet be defined during life by any physiological test or anatomical measurement.

(*d*) Finally, from a technical point of view the surgeon is liable to produce many incidental lesions which cannot be ascertained during the patient's life.

We are concerned here mainly with the last problem, that is to say, the extent of uncertainty in the lesions which may occur during the various stages and techniques of psycho-surgery. Some of these techniques have their special causes of error, but all of them, since they deal with the brain, have in common some general sources of error. The same factors are met in general neuro-surgery, for instance when taking out a tumour of the brain, but there is a tendency to overlook them in the more limited field of psycho-surgery, because of its apparent facility. In fact, if the surgeon wants to estimate what actual damage he is responsible for in the frontal lobes, he has to be very well aware of many pitfalls, and must take pains to perform as scientific an operation as possible. If not, it becomes very hard indeed to establish reliable correlations between the operation and its results.

We believe the simplest way of classifying the causes of error is as follows :

I. Extra-cerebral stages of the operation.
II. The cerebral stage.
III. Post-operative stage.

The basis of the present study is a series of 100 consecutive patients on whom were performed 13 lobotomies, 76 topectomies and 11 cortical undercuttings during the last three years ; all of them are personal cases.

I. Factors of Error in the Extra-cerebral Stages.

These are the least obvious, but by no means the most negligible. Fortunately most of them do not usually leave any lasting effect. Let us discuss them in their natural chronological order.

(1) *Epileptic fits* during the operation. In our experience these never occur during general anaesthesia. They were observed in patients under local anaesthesia, but very rarely indeed, and then in spite of the injection of sodium bromide, which is given intravenously as a routine. In our series three patients developed fits during the operation ; two of them were chronic epileptics, and the other had never had a fit before. We do not believe that these isolated fits can leave any permanent mental change, such as is sometimes seen after electro-shock therapy (and the same can be said of the isolated fits observed during the 24 hours following the operation). A generalized fit developing during an operation may, however, be the cause of diffuse haemorrhage leading to cortical damage. To prevent this complication good technical control is necessary. When a fit occurs while the dura is still open, both frontal lobes swell markedly and the veins become very much larger, the blood pressure inside them increasing tremendously. The only thing to do is to pack firmly the whole surface of the brain with cotton wool pads in order to prevent rupture of the more important emissary veins, to wait quietly until the end of the fit, and only then to secure haemostasis. In our series no diffuse meningeal haemorrhage was observed either operatively or post-operatively.

(2) We come now to the factors of error directly related to the extra-cerebral stages of the operation : turning the bone-flap, opening the dura, *opening the subarachnoidal space.* All these stages disturb the physical balance of the brain, which in turn usually implies some changes in the cerebral vascular system. The often beneficial effects of a so-called " decompressive flap " have been known for long. Such a flap usually is turned in the right fronto-temporal region, and subtemporally the dura and arachnoid are opened. In three types of diseases at least this simple operation may change the whole clinical picture :

(*a*) Intractable pain in cancer cases, although the sedation rarely lasts more than one or two weeks.

(*b*) Some cases of mental backwardness in which a certain excess of cerebro-spinal fluid or brain oedema (so-called encephalitic state) is found at operation.

(*c*) Epilepsy : Sometimes the fits disappear for several months after the decompression.

These instances prove that some changes in the reactions of the brain are possible even without touching the frontal lobes at all.

(3) *Actual lesions of the brain.*—Even during the extra-cerebral stages, there is a possibility of producing damage of the brain with permanent effects. It is liable to occur especially in patients more than 60 years old, with a high blood pressure and signs of arterial sclerosis. Often in such patients " operative shock " is loosely alluded to. In fact, following any abrupt variations in blood pressure, the possibility of haemorrhages or softening in the cerebral hemispheres is to be feared. The point is well illustrated in one of our patients. His pre-operative systolic blood pressure was 160, and he was complaining of violent pain in one side of the jaw, due to a maxillary carcinoma ; mesencephalic tractotomy was tried, but could not be performed on account of an abnormally large occipital lobe difficult to retract ; meanwhile the blood pressure went first up to 220, then down to 140 ; from the day following the operation until he left the hospital two months later he was completely free from his

terrible pain but, during that time, he showed a definite state of slight mental confusion with sphincteric disturbances. We believe that such a case strongly suggests the occurrence of lasting vascular damage, probably not closely related to the site of the operation. Similar complications may occur in patients with low blood pressure, anaemia and dehydration (cancer cases, drug addicts). Fig. 1 shows a cortical haemorrhage discovered at post-mortem six weeks after an operation in which the only abnormality was a rise in blood pressure.

In such cases it becomes extremely difficult to assess the post-operative results. The best thing to do is to try and prevent these complications by giving a blood transfusion during the operation. In the following days, if

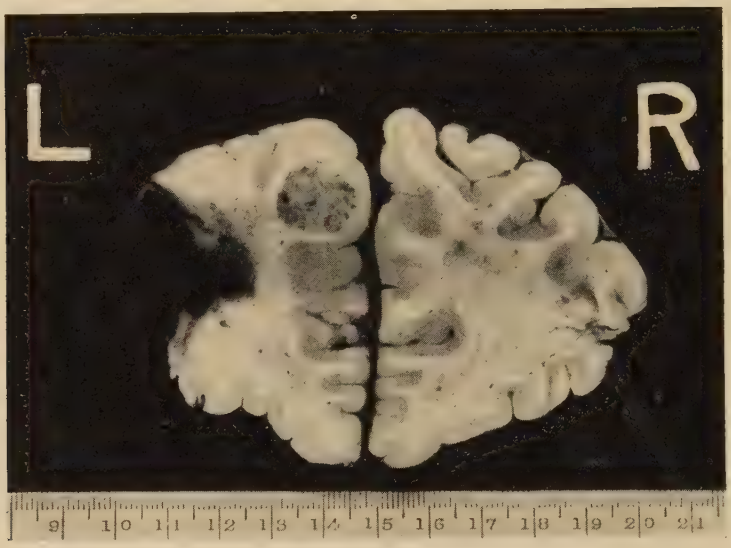

FIG. 1.—Bilateral topectomy of areas 45. Intestinal carcinoma. On the left side, post-operative cortical haemorrhage and metastatic nodule. (Personal case; pathological examination by courtesy of Prof. Meyer.)

there is concern about the blood pressure and the condition of the heart, suitable drugs and plasma should be given intravenously as long as is necessary, but the rise in blood pressure during or just after the operation is still a problem unsolved, by us at least.

(4) Finally, when analysing the post-operative mental changes of a cancer case submitted to lobotomy or topectomy, the possibility of cerebral *metastasis* should not be forgotten. Thus the patient mentioned above exhibited mental confusion until the time of his death; post-mortem examination of the surface of the brain did not disclose anything striking; but Prof. Meyer, to whom the specimen was sent, discovered eighteen small metastatic nodules disseminated within the two hemispheres (Fig. 1).

To sum up. The "extra-cerebral" factors of error are many, but not very important in patients under 60 years of age. They are most frequent in elderly patients with arterial disorder. In such cases, therefore, in our opinion, one should use the simplest techniques, cortical undercutting or open leucotomy

for instance, in preference to topectomy, which requires larger and more time-consuming bone openings.

II. Factors of Error in the Cerebral Stage.

During this stage the factors of error are important because all of them lead to permanent damage larger than is the surgeon's aim. It is hoped that describing them at length may help towards reducing their frequency. They are present in every technique of prefrontal surgery, but in some more prominently than in others.

We shall classify these cerebral factors of error according to their causes.

A. Direct Lesions.

(1) Section of subarachnoid and subdural veins.
(2) Section of cortical arteries.
(3) Opening of lateral ventricles and wounds of the deep grey nuclei.
(4) Section of unintended white fibres.

B. Indirect Damage.

(1) Cortical.
(2) Subcortical.
(3) Diencephalic.

A (2) and B (3) in our opinion are the most significant, especially the latter, which is less detectable than the former.

A. *Direct Lesions.*

(1) *Section of Veins.*

On each side the venous output of the frontal lobe is concentrated in two or three large veins which leave the cortex, and after a free subdural route enter the superior longitudinal sinus. Nothing is more variable than their volume, their number and their length. Often there is a large prefrontal vein lying roughly at the junction of Brodmann's areas 9 and 10, and a similar one 2 or 3 cm. further back; their average length is 1 to 2 cm., but often veins of 4 or 5 cm. in length are met on each side. In spite of these variations it is our impression that larger and more numerous prefrontal veins are observed both in chronic mental patients and in patients with chronic epilepsy or chronic intractable pain. Reviewing our operative notes, we find that an "abnormally large venous development" was observed in 26 of our 100 cases. Now, the subjective impression of "normality" during life is based on inspection of the frontal lobes in head injuries and cases of optic arachnoiditis, pituitary tumours, and, generally speaking, tumours with little rise in intracranial pressure—an "abnormal" venous network was noted in only 8 per cent. of such cases. However that may be, our present interest is:

(*a*) How many subdural veins are cut; and
(*b*) What effect is this likely to have on distant parts of the frontal lobes?

It should be stated at once that the so-called "blind" techniques are not likely to damage the emissary veins. Neither transorbital leucotomy, nor lobotomy performed through a lateral approach, runs the risk of cutting through large subdural veins, since the entry point is far away from the longitudinal sinus. On the other hand, "open" techniques (apical lobotomy, cortical undercutting, topectomy) inevitably lead to some interference with part of the venous drainage of the brain, and particularly topectomy, where the dural opening is the largest. The anatomical and physiological effects depend entirely on the relative number of veins interrupted. We believe that in topectomy sufficient posterior drainage of the frontal lobe is usually left intact to prevent haemorrhagic passive oedema, but such a complication is observed occasionally. (In neuro-surgery it is seen more often in the occipital lobes, where the drainage tends to depend upon one large vein.) It happened twice in our 100 cases. One was a case of phantom limb, in which the bleeding was so marked that the operation had to be stopped before the cortical resection ; a few days later, when the wound was reopened, large blood-clots were found in the white matter of both frontal lobes. The patient survived, but with a definite impairment of his mental faculties. The second case was one of Parkinson's disease, in which many frontal veins had to be clipped on both sides. The patient's condition grew worse, and on reopening the wound bilateral oedema of the frontal regions was found and death followed two days later. (No post-mortem examination was possible.)

Thus one can clearly imagine the occurrence of intermediary cases in which, without leading to life-endangering complications, severing of veins disturbs the frontal lobes to a certain extent and creates an indeterminable factor in evaluating the post-operative results. In practice this cause of error can be reduced easily enough if one is very careful to conserve as many veins as possible, at least on one side. Usually a precise evaluation of the venous drainage is possible, even before making an opening in the dura, through which the larger veins can be seen, and hence spared as much as possible during the resection, especially of areas 9 and 10 on the convexity of the brain. In our technique for the resection of areas 24 and 32 both sides are excised through a unilateral opening of the dura which exposes the falx ; we think it extremely improbable that an incomplete venous interruption on one side only is likely to leave any permanent frontal disturbance. Usually a quite sufficient drainage is secured by the veins passing down to the Sylvian fissure and the spared veins going to the superior longitudinal sinus (Le Beau and Pecker, 1950*a*).

The foregoing concerns only the prefrontal veins in their subdural aspect. Now we have to consider the prefrontal veins in their arachnoidal and pial aspects. Generally speaking they are smaller, since by convergence they are going to form the subdural veins. This means that each of them is responsible for a smaller territory. Again intracortical anastomoses are numerous. Therefore the question of interruption does not matter much ; but if they are cut uncautiously a superficial haemorrhage can be produced, and, as we shall see presently in more detail, untoward effects are possible. In respect of this problem of haemostasis, therefore, the open methods are by far superior to the blind ones.

(2) *Section of Cortical Arteries.*

In any prefrontal operation one has to divide a variable number of superficial or deep cortical arteries, resulting in a suppression of function in the corresponding cortex. It is not a very important point as long as the arterial interruption is limited to the smaller superficial terminals, because their territory is not likely to go beyond the area of resection for more than a few millimetres. When a larger artery, hidden in the depth of a sulcus, is cut or coagulated, it may cause interruption of cortical function for several centimetres beyond the edges of the resection.

At once we see here the main disadvantage of the "blind" techniques (latero-frontal approach of Freeman and Watts (1942), and transorbital approach of Fiamberti (1949) and Freeman (1948)) : fairly important arteries within sulci may be cut with unpredictable resultant cortical damage. Furthermore, haemostasis is difficult or impossible, and a special factor of cortical compression by haemorrhage may be added. This danger is even more pronounced in transorbital leucotomy than in the classical lateral approach, but in the latter, when one wishes to perform a complete lobotomy, arteries in abnormally deep sulci may be cut. This is a well-known frequent cause of post-operative death, and a more frequent cause of variable cortical damage (Le Beau, 1948*b*).

In this respect the advantage of the open techniques (Lyerly-Poppen, Pool, Scoville) is evident, in the sense that one sees what one does ; the more important arteries are easy to avoid and any bleeding can be checked. The respective advantages and disadvantages of topectomy and cortical undercutting, both open techniques, require fuller discussion.

In topectomy the section of many cortical arteries is necessary. It is, however, possible to avoid the main arteries near the limits of the resection if they are superficial. In practice there are always two or three largish branches on each side which are hidden in the sulci and cut, although they should have been respected because their territory lies mostly outside the limits of the proposed topectomy. This means that when one speaks of a cortical resection of, for instance, 4 times 3 = 12 square cm., the actual surface deprived of function is in all likelihood nearer to 5 times 4 = 20 square cm.

Cortical undercutting has the same disadvantage, but to a lesser degree, because the area of resected cortex is much smaller. At the limits of the undercutting, if one wants to interrupt the cortico-cortical connections, one has to damage the intra-sulcal grey matter, with probable involvement of some arteries in the sulci. This has especially to be feared in old people (over 60), for in such cases the brain very often seems to be shrunken with deep sulci, the volume of the white matter looking much smaller than usual.

In order to cut as few cortical arteries as possible, we find it a great advantage to perform topectomy by a sort of subpial dissection which we call *decortication*. Under direct visual control, with a fine suction tube, aspiration of the whole grey matter corresponding to the chosen area is performed. Fine holes are burnt in the pia with coagulation forceps ; through these holes the tube is inserted and the cortex aspirated over a radius of 1 to 2 cm., until a sulcus with its vessels is met ; the same thing is repeated all over the proposed area

of resection. Of course there is inevitably some slight bleeding due to the pial vessels, but this is very easily checked. When the decortication is finished, in every one of the 5 or 6 subpial cavities thus created one deposits some gelfoam to take the place of the aspirated cortex. Strictly speaking it is not a subpial dissection because the pia can be resected too, without harm so long as it does not contain any cortical vessel of significant size. The larger the decorticated areas are, the simpler is their haemostasis and the quicker the operation.

This technique is used in our hands mostly when performing topectomy of areas 24 and 32, where it is imperative to protect the ascending vessels going from the anterior cerebral artery to the mesial aspect of areas 10 and 9. It can, of course, also be used in orbital topectomies. Now we use it more and more in topectomies of areas 9 and 10, in which we feel it gives us a physiologically more limited operation. Its main drawbacks are : (1) the difficulty of being certain of aspirating the whole cortex, especially in the deepest sulci ; (2) the danger of aspirating and damaging medium-sized arteries. Both, in our opinion, are related to another very important variable factor, namely, the *consistency of the brain*. On account of this it is necessary to be able to vary the strength of the aspiration. In many patients the brain is soft and the arteries are not fragile, and moderate aspiration performs decortication quickly and safely, but in other patients the technique is not so simple. Sometimes, in elderly patients, the cortex is compact and adheres to the pia, which contains hardened and fragile arteries ; aspiration in such cases should be stronger when remote from the sulci. Sometimes, in younger patients, the brain has a tendency to be oedematous and congested, and the small arteries bleed easily ; aspiration should be weak in general, and possibly stronger when near the sulci, with their larger and more resistant arteries. Recently Le Gros Clark suggested the " peeling off " of the pia, thus devitalizing the underlying cortex. We tried it and found the process not very practical in human beings, especially in the sulci.

Whatever technique is adopted, precise and prompt haemostasis is necessary. Even small subarachnoid or subpial haemorrhages may disturb cortical function to a great extent. For instance, we are able to quote one case in which decortication of areas 24 and 32 was performed under direct electrocorticographic control ; a small haemorrhagic infiltration produced in area 9 behaved at once as a very active epileptic focus (a few days later, however, the electroencephalogram did not show any abnormality).

To sum up, as far as vascular damage is concerned, we firmly believe that only the open techniques should be used, and topectomy with some precautions is likely to give the best delimited cortical destruction.

(3) *Wounds of Lateral Ventricle and Deep Grey Nuclei.*

There is little to say under this heading. The importance of bilateral damage to the basal ganglia as a cause of post-operative death was demonstrated by Meyer and McLardy (1949). They found damage to the ventricles to be, *per se*, irrelevant clinically. We likewise do not believe that extension of the lesion into the anterior horn introduces many lasting causes of error,

provided there is no intraventricular post-operative bleeding. "Open" methods, therefore, are much safer in view of this latter possibility than the blind ones, but we wish to stress again the frequency, not to say the constancy, in patients over 60, of enlarged frontal horns and diminution of volume of both frontal lobes, with no rise in intracranial pressure. This appearance is found in patients with mental diseases as often as in other groups (e.g., intractable pain). In such cases a lobotomy belonging to the posterior or medium variety (near the plane of the coronal suture) will always open the ventricles. Anterior lobotomy, similar to the "rostral" leucotomy of McKissock (1949), will avoid this as a rule. Cortical undercutting of the mesial side of the frontal lobe (areas 10, 12, 24 and 32) must often open the mesial wall of the frontal horn. Topectomy, whatever its location, should not endanger the ventricle.

Much more important than opening into the ventricle is the creation of direct lesions in the caudate nuclei, and even sometimes in anterior parts of the putamen and the globus pallidus. In several publications Meyer and McLardy (1949, 1950) have described such post-mortem findings. There is no doubt that, besides the danger of death, such lesions produce an extremely large factor of unpredictability of the post-operative mental disturbances. Here, again, the older the patient the more fragile his vascular system and the greater these disturbances.

Fortunately it is easy to avoid all those complications by adhering to the following rules :

(*a*) No lobotomy should be performed posterior to the plane of the coronal suture.

(*b*) No lobotomy should be performed by a blind method.

(4) *Section of Unintended White Fibres.*

Two special factors of error are to be taken into consideration when the white matter is interrupted under direct visual control. The first has to do with the relative volumes of white and grey matter of the brain. When a selective leucotomy (Dax, Reitman and Radley-Smith, 1948) is performed on a shrunken brain, with deep sulci and large ventricles, the same length of cut destroys more fibres than in a normal brain ; thus the section may be physiologically more extensive than the surgeon believes during the operation or observes in a post-operative X-ray picture.

The other and very important limitation to selectivity appears in cortical undercutting of orbital and cingular surfaces. A part of area 10 has to be traversed in both cases and many of its white fibres are interrupted. This technically unavoidable factor is a definite disadvantage when comparing undercutting of the orbital and cingular regions with topectomy of the same areas.

B. *Indirect Damage to the Brain.*

This chapter is concerned with the effects of protraction and retraction of the brain, depending on the surgeon's skill, the instruments he uses and the physical properties of the brain substance. Only the last two factors lend themselves to a general analysis of the anatomical consequences.

(1) *Cortical Damage.*

We have already described some indirect cortical lesions which may follow either an important haemorrhage (subarachnoidal or subpial haemorrhage), or too strong an aspiration. A more indirect kind of damage may be caused by retractors. Here again it will be found more accentuated in elderly patients with vascular fragility.

In topectomy of areas 9 and 10 or of areas 8, 45 and 46 no retractors are used, and this source of error does not exist, but in topectomy of areas 11 and 47 one has usually to retract the area 10 region backwards, with a possibility of damage, which may be significant in its results when bilateral. In our topectomy of areas 24 and 32 a retractor has usually to be placed on the mesial aspects of area 9, but only on one side, since resection on both sides is practised through a unilateral transdural approach (either right or left); the risks of significant unintended bilateral damage to "area 9 region" is thus much lessened (Le Beau and Pecker, 1950*a*).

In cortical undercutting, intracerebral exposure is achieved by means of retractors or the spatula forceps described by Scoville (1949). There is no doubt that the less "open" the leucotomy, the more force has to be exerted with one of the retractors against the deep part of the undercut cortex; this, of course, is of little importance, since the aim of the operation is precisely to suppress the functions of this cortex. It might be more treacherous when one considers the edges of the undercut area. In fact the main drawback lies in the indirect effect of the lower arm of the retractor, with its possibility of damaging deep structures below the plane of the cut.

Finally, the instruments used in performing haemostasis of the cortex have to be considered. As regards the choice between clips and diathermy, what matters most is their comparative scarring effects. We do not believe it differs significantly. Firstly, when a wound is reopened months or years later there is no appreciable difference in the apparent volume of the scar tissue whatever technique was used; in fact, every silver clip is the centre of a hard scar. Of course the use of tantalum clips should lessen the tissue reaction. Secondly, electroencephalography performed a few weeks after the operation did not show more alterations with one method than with the other; in a series of 56 topectomies (which leaves out the epileptics before the operation) only three exhibited a lasting post-operative abnormal E.E.G. In practice we nearly always use diathermy in performing topectomy, and we feel confident that it is not a cause of post-operative epilepsy. Therefore there is little ground for holding it responsible for post-operative mental changes.

(2) *Subcortical Damage.*

By this term we mean lesions of the white matter located deeper than, or further back than, the actual lesions seen at operation.

Pool's topectomy is in practice immune from this hidden extension of the operation. Sharp scissors are usually employed to cut through the white matter at the base of the resected area, so that there is little likelihood of producing traction and haemorrhagic foci. If decortication is used, aspiration would

have to be very strong to cause lesions in the white matter more than a few millimetres away.

All leucotomies, however, are open to this objection as to the indeterminable amount of damage to white fibres, to a various extent, according to the type of operation.

Strangely enough, the old-fashioned " blind technique " of lobotomy, if it is to be rejected on account of its risks of cortical damage, offers fewer grounds for criticism with regard to the white matter, the main reason being that rather sharp instruments are used (this includes the classical " blunt " leucotomies). Cutting through the white matter is clean enough, and as long as no significant vessel is met (i.e., no cortex or basal nucleus) the risks of haemorrhage are small.

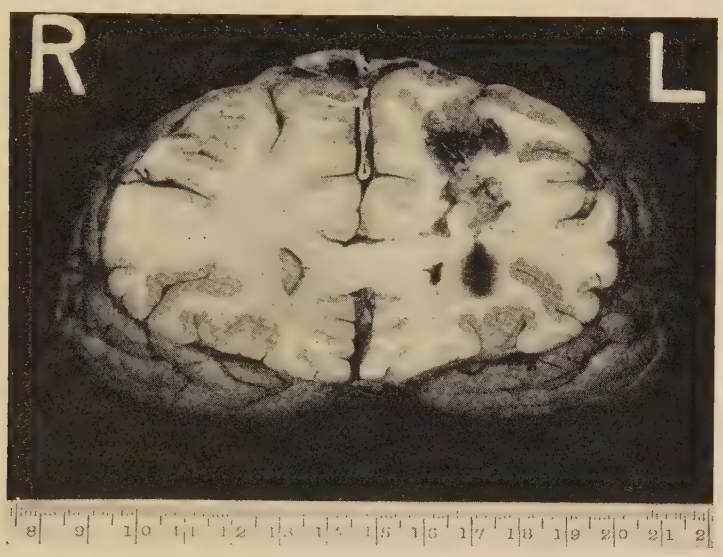

FIG. 2.—Unilateral lobotomy. Post-herpetic facial neuralgia. Aged 82. Haemorrhage reaching head of caudate nucleus behind the leucotomy plane. (Personal case ; pathological examination by courtesy of Prof. Meyer.)

On the other hand, in transorbital lobotomy the main drawback is a lesion of the white matter more limited than one thinks ; it has been shown that the frontal lobe, which is mobile, may " follow " the rotating needle to a certain extent.

In open techniques for leucotomy, such as the lobotomy of Lyerly-Poppen (1944, 1948), or Scoville's cortical undercutting (Scoville, 1949), the " cutting " instrument is a fine metallic sucker tube. It cuts through the white matter without difficulty when the consistency of the brain is soft, but often, especially in elderly patients, the white substance is fairly hard, and cutting through it with a sucker tube does imply some traction and danger of producing haemorrhagic zones on both sides of the plane of section, the more so if the aspiration is unnecessarily strong. One of our patients, aged 82, died suddenly two weeks after a unilateral lobotomy ; the brain was sent to Prof. Meyer, and sections disclosed, further back, a haemorrhage of the white matter invading the head of the caudate nucleus, while during the open operation nothing abnormal was observed in the plane of section (Fig. 2).

Generally speaking, we believe there is a definite danger of causing unseen operative lesions by using too strong an aspiration on leucotomies. Of course, death will only very exceptionally be the consequence of such lesions when limited to the white matter, but one can see how the possibility of their occurrence upsets the apparent precision of selective undercutting or " open " lobotomy.

(3) *Diencephalic Indirect Damage.*

In our opinion this is an extremely important cause of error, difficult to assess, but the possibility of which must always be thought of every time there is a displacement of the frontal lobe as a whole. Such treatment creates a stress on the so-to-say hinge which unites the frontal lobes to the anterior hypothalamus, as was shown by Clovis Vincent (the thalamus being in such *mechanical* relationship more with the temporal lobe). If a haemorrhage is produced at this region the outcome is usually fatal. Even without histologically demonstrable lesions, functional disturbances of hypothalamic nuclei, when they last long enough, may not be compatible with life (Jefferson, 1942) ; less severe ones may lead to temporary symptoms. The possibility of minute anatomical lesions leaving a permanent disorder cannot be ruled out, and constitutes a grave factor of uncertainty.

In general neurosurgery such complications are mostly observed after surgical attack on tumours of the suprasellar region : huge pituitary adenomas, cranio-pharnygiomas, olfactory and suprasellar meningiomas and gliomas of the anterior part of the third ventricle. Sometimes they are seen also after a simple exploration of the optic chiasma in patients with arterial and blood-pressure disorders. During tumour resections the hypothalamus is liable to be damaged directly, or its arterial supply interrupted ; but simple retraction of the frontal lobe, especially when the retraction lasts a long time and when the frontal lobe is large and dense, is enough to produce very considerable post-operative disturbances. We will study them in six groups, every one of them having some bearing on mental status.

(a) *Metabolic disturbances.*—Hypothalamic regulation of water, fat and sugar metabolism is well known to exist. Some patients die a few weeks after psychosurgery in a state of progressive emaciation, often with spreading bedsores, and sometimes uraemia. The same symptoms were observed in cases of head injury Jefferson, 1942, Clovis Vincent, 1937.

(b) *Disturbance of consciousness.*—There is no need to emphasize this aspect of hypothalamic disorder, though the expression " diencephalic disorder " would seem to be preferable. Penfield, Jefferson and others have developed this thesis, and we had occasion to write on the same subject in 1942 (Jefferson, 1942 ; Le Beau, 1942 ; Penfield, 1946).

(c) *Other mental disturbances.*—These are frequently observed during the first post-operative days or even during the operation, as Foerster (1933) first mentioned : mental confusion, disorientation, hallucination, uncontrollable agitation, hypomanic state. They may clear up or lead to obscuration of consciousness and progressively increasing coma. The experience of thala-

motomy introduced by Spiegel and Wycis (1947) brings strong arguments in favour of the importance of the diencephalon in such mental disturbances.

(d) *General vascular disturbances.*—Even without an important loss of blood hypothalamic lesions at operation are sometimes followed by an extreme and lasting fall in the general blood pressure with signs of peripheral vascular collapse. This condition is not necessarily fatal, but its successful treatment calls for long and complex intravenous therapy (blood, plasma, adrenaline) (Vincent, Guillaumat and Le Beau, 1937).

(e) *Vascular disturbances of the brain.*—Diencephalic and hypothalamic operative lesions may cause a striking phenomenon called *acute oedema of the brain*. It is a tremendous swelling of both frontal lobes with arterial dilatation, first described in 1935 by Clovis Vincent (1935). We studied brain oedema and its production by diencephalic damage in our thesis published in 1938. Then and later in London we were able to study acute brain oedema in experimental studies performed on dogs and cats (1948). Acute brain oedema in man is less often fatal when following a diencephalic lesion than when following a lesion of the lower part of the brain stem, which is liable to cause at the same time an important rise in general blood pressure (Le Beau, 1948*a*; Vincent, 1935).

(f) *Electrical disturbances of the brain.*—In the last few years it has been shown that the electrical activity of the cortex can be changed by stimulation of some parts of the brain stem, hypothalamus and thalamus (Dempsey and Morison, 1942; Jasper, and Droogleever-Fortuyn, 1947; Moruzzi and Magoun, 1949; Murphy and Gellhorn, 1945*a*, 1945*b*). Even before that stage of electrical investigation some neurosurgeons had good reasons to believe in the primary importance of the hypothalamo-mesio-frontal region in the production of fits of generalized epilepsy. Thus, we described a special anatomical group of frontal gliomas, called olfactive gliomas, after total extirpation of which death often followed from status epilepticus (Le Beau, 1942).

These six groups of disturbances are often associated. The mere possibility of any of them occurring makes one slightly critical of some conclusions regarding the importance of the frontal lobe, for instance, in the autonomic field. The excellent recent study of McLardy (1950) on post-operative death after lobotomy should be discussed from this point of view. Perhaps some of the results found by Rylander (1939) in his classical study of mental impairment after unilateral frontal damage should also be considered as due to hypothalamic disturbance, because many of Rylander's cases were operated on for large and technically difficult frontal tumours.

On the other hand, it could be argued that the so-called hypothalamic mental disturbances are, in fact, due to direct frontal damage caused by retraction of the frontal lobes or by impairment of its vascularization. In surgery of suprasellar tumours, however, one frontal lobe only is retracted; furthermore, many neurosurgeons, like ourselves, believe that in difficult cases it is less harmful to resect one prefrontal lobe than to retract it; one is more afraid of damaging indirectly deep structures than of resecting cerebral cortex.

To sum up, the hypothalamo-frontal connections are not only anatomical (Le Gros Clark, 1948), but also mechanical. There is thus a definite possi-

bility of producing hypothalamic damage and consequent mental changes when the frontal lobe is uncautiously moved "en masse." The various techniques of psychosurgery are not equal in this respect. Topectomy is practically immune from this danger, except perhaps in orbital resection, when the bone flap cannot be made low enough on account of a very large frontal sinus; in such a case we should strongly recommend cortical undercutting. Cortical undercutting, when orbital or cingular, should not go too far postero-mesially. The same applies of course to lobotomy, which is a very dangerous operation when performed posteriorly and mesially. All the leucotomies (this includes cortical undercutting as well as lobotomy) may lead to hypothalamic or even thalamic damage when the frontal lobe moves with the instrument used to section the white fibres. Once more it should be emphasized that such complications are specially to be feared in elderly patients with high blood pressure and arterial disorders.

III. Factors of Error in the Post-operative Stage.

Let us suppose that an ideal technique allows the surgeon to destroy or interrupt a certain part of the cortex, and this part only. The next problem is: What is the anatomical definition of this part of the prefrontal lobe. And to begin with, are there such things as distinct prefrontal areas?

Recently Bailey (1950) has delivered several attacks on the excessive parcellation of the frontal lobes, and advised against further use of Brodmann's map. His thesis receives strong support from his criticisms of previous anatomical studies and from his personal work; there is no doubt that the German architectonic school sometimes went too far. It seems difficult, however, to subscribe entirely to his point of view.

Firstly, even if there were no such things as distinct prefrontal fields, Brodmann's numerals are so well known and so practical that we would strongly recommend continuation of their use in a purely topographical sense; they shorten description in a most convenient way.

Secondly, studies on human material by Beck, McLardy and Meyer (1950) have demonstrated clearly that there are several prefrontal fields differing from each other in their central connections as well as in their histological structure. These workers also demonstrated, however, the difficulty of identification of border zones between fields and the variability of the extent of even the fields which are easier to recognize. We will see presently the great practical importance of these facts.

In conclusion it seems to us that there is no good reason yet to abandon attempts to express in terms of Brodmann's map the anatomical extent of our cortical resections, but the way to achieve this purpose is not simple. At present we can see only three possibilities: pathological examination, measurements during the operation, and radiological measurements.

(1) *Pathological Examination.*

During life this can only be performed on the operative specimens from topectomies (in which the cortical resection should be done quickly and neatly

with sharp scissors). Even so, there is reason to believe that no precise study will be possible. In our practice at least all the operation specimens are more or less infiltrated with blood, and, perhaps wrongly, so far we have not tried to have them histologically investigated for architectonic identification.

We are left, therefore, only with post-mortem specimens from operative deaths. These are a rare occurrence in prefrontal surgery and, anyway, would not serve our purpose, since naturally no significant post-operative mental data are available for study in such cases. (They are still very valuable often for anatomical studies of prefrontal connections.) Late deaths due to disease more than six months after the operation lend themselves to a comparative study of the mental changes and the anatomical extent of the operation. Such cases are not easy to find, except among the poorly improved cases still under observation in mental institutions at the time of death. McLardy and Meyer (1949) succeeded in making the most of such material in their clinico-anatomical analyses. No doubt topectomy will allow of further interesting correlations. Nevertheless, two additional causes of error must be stressed : one is clinical, i.e., the physiological complexity of the psychotic patients who die in mental homes ; the other is anatomical, when the patient dies long after operation from intercurrent disease, causing additional changes in the brain or accompanied by the natural ageing of the brain.

Thus pathological post-mortem examination, though invaluable and decisive, will not prove practicable in more than a few significant cases. As we shall see briefly later, it is difficult at the present time to think of any method other than a statistical one for correlating types of operation and psychological changes. Some other way of assessing the anatomical extent of the operation should be found. We believe it possible, with reasonable precision, by the use of careful post-operative radiological study. (See section 3 below.)

(2) *Surgical Measurements.*

We should explain first why measurements taken during the operation itself are hardly reliable. The usual landmarks are the coronal suture, the orbital roof, the Sylvian fissure, the corpus callosum, the falx, and the frontal horn.

The coronal suture has no fixed relation with the brain structures, and is seldom actually seen on the bone at operation.

The orbital roof is far from being a plane ; its medial aspect is part of a fossa, variable in depth and width. Its external part, however, is usually more regular, and gives a roughly reliable landmark.

The Sylvian fissure, which we formerly suggested, is not practical, because it is too far from the more frequent sites of the frontal resection. There is no need to turn a flap extending laterally more than 5 cm. from the midline in orbital, peri-callosal, or " area 9 and 10 " topectomies. The Sylvian fissure, on the other hand, proved convenient in resection of areas 45 and 46 (performed twice).

The genu of the corpus callosum is a very important landmark for the resection of areas 24 and 32 in our peri-callosal topectomy, but its depth and length are very variable, as we found on many occasions. There is, however,

no need to discuss this further until we know something of the precise anatomical variations of the mesio-frontal areas.

The falx cerebri of course is in the midline, but during the course of an operation the brain is exposed to many variations in its volume. This makes measurements from the falx less reliable than a radiological checking a few days later.

There is no fixed position of the frontal horn, the variations of which are now well known. We would just emphasize once again how often it is enlarged and extends far forward in elderly patients with shrunken brains.

Finally, the ideal landmark for studies such as the present ones may be the foramen caecum, which Meyer (1948) and his associates chose as a reference point. For although we do not find it easy to recognize during operation, measurements from this point prove simple enough in X-rays of the skull.

(3) *Post-operative Radiological Study.*

This was not practicable before the pioneering work of Beck, McLardy and Meyer (1950). For the first time we have here systematic measurements of the cytoarchitectural length of areas 11, 10 and 9 near the midline. The reference point is the foramen caecum, which corresponds to the anterior limit of the base of the crista gallica, and to the posterior margin of the frontal bone, easily seen on well-centred lateral X-ray views of the skull. Here we shall be concerned with the extremes of variation in length which they have established (always bearing in mind that up to now only a few hemispheres have been analysed at the Maudsley Laboratory).

Now let us consider area 10. If by some technique we can measure precisely on the X-rays the limits of our cortical resections, in a large enough number of cases, we shall be able with a reasonable degree of probability to separate a group including the greater part of area 10 from a group including little of it.

The opaque substances used as landmarks in prefrontal surgery belong to two groups: (1) metallic clips or wire; (2) iodized oil.

Putting silver clips along the edges of the resection, as in Pool's cases (Heath and Pool, 1948; Pool, 1949*a*, 1949*b*), seems by far the simplest and most reliable technique. We use this method in our topectomies of the convexity (including areas 8, 9, 10, 45 and 46), but clips cannot be placed easily at the limits of a leucotomy; and in topectomies of areas 24, 32, 12, 11 or 47 it is not simple to put them exactly at the farthest limits of the resection. Finally, if silver clips are intended to define the amount of cortical resection, they should not be used on the dura, the haemostasis of which is often difficult when large subdural veins are opened near the longitudinal sinus. In Figs. 3, 4, 5, 6 and 7 typical examples of different topectomies are shown.

A metallic loop of tantalum wire is used by Scoville in his cortical undercuttings. We do not find this technique very reliable, having experienced difficulties in placing the wire right along the curve of the undercut field. At this point another factor of uncertainty in cortical undercutting should be stressed again. An undercutting of area 10 undercuts only area 10, whereas

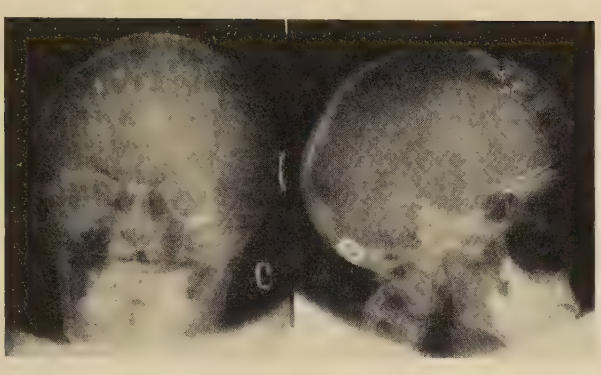

FIG. 3.—Silver clips marking the limits, frontal and lateral, of a topectomy of areas 8-9. (Sexual impulsions.)

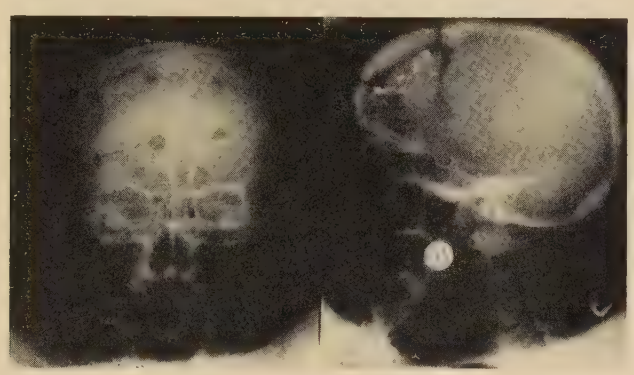

FIG. 4.—Silver clips. Topectomy of areas 9–10. (Phantom limb.)

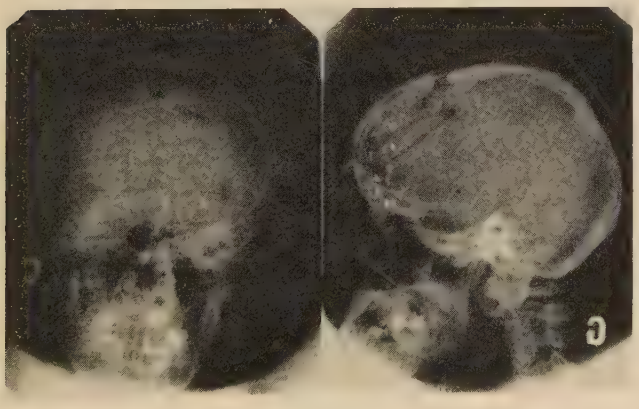

FIG. 5.—Silver clips. Topectomy of areas 10-11. (Anxiety state.)

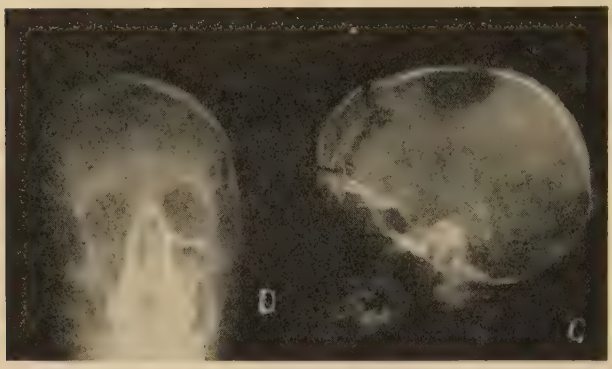

FIG. 6.—Silver clips. Topectomy of areas 11–47. (Psychomotor akinesia.)

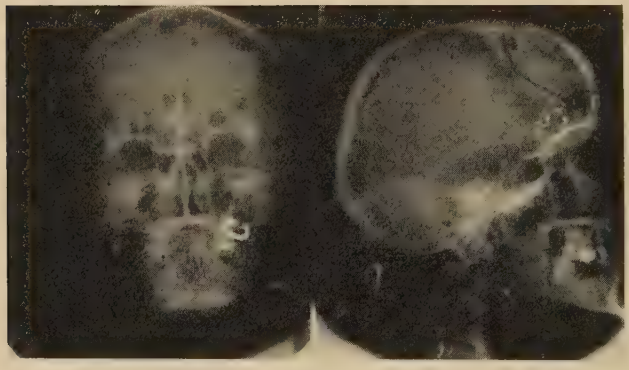

FIG. 7.—Silver clips. Topectomy of areas 32–12. (Epilepsy.)

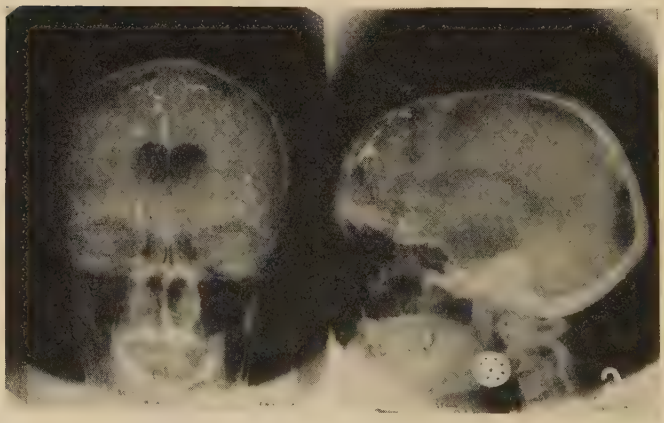

FIG. 8.—Bilateral lobotomy. Diffusion of free lipiodol into the subarachnoidal spaces. (Schizophrenia.)

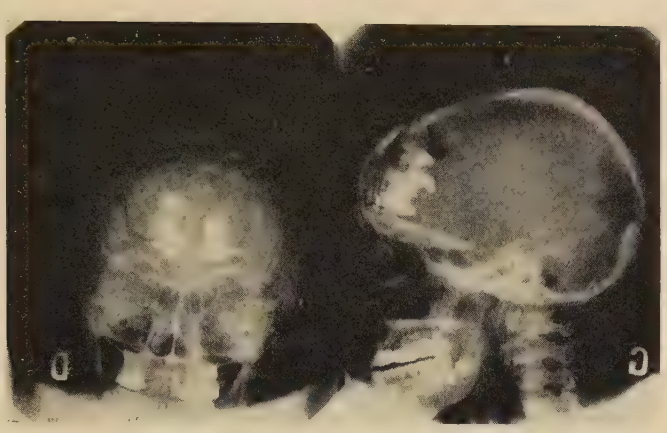

FIG. 9.—Gelatin-lipiodol. Bilateral topectomy of areas 10 by decortication. (Anxiety state.)

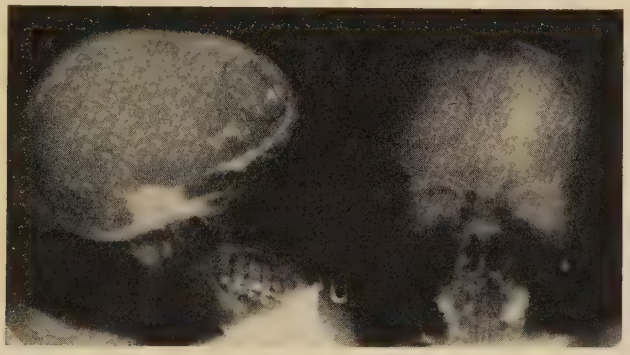

FIG. 10.—Gelatin-lipiodol. Bilateral undercutting of areas 10 and 11. Clips on cortical opening. (Schizophrenia.)

This case shows a possible additional cause of error in undercuttings : if the surgeon does not keep strictly close to the inner surface of the grey matter (which is not always easy) there is a danger of cutting white fibres deep enough to belong to the thalamo-prefrontal radiation for instance. In the case illustrated in Fig. 10, the section of fibres connecting the thalamus and area 9 has to be considered.

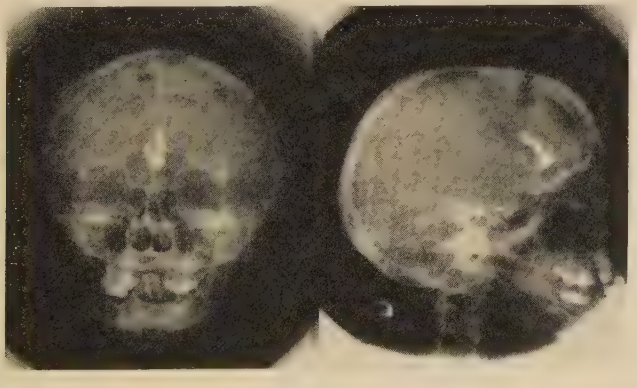

FIG. 11.—Gelatin-lipiodol. Bilateral topectomy of areas 24 and 32. (Obsessive neurosis.)

an undercutting of either the orbital surface or the mesial surface of the frontal lobe *always undercuts also a large part of the polar region* (area 10), as remarked previously.

Lipiodol has been used by many surgeons since it was introduced by Freeman and Watts (1942). It gives rise, however, to erroneous interpretation ; it is too fluid and often escapes into the subarachnoidal spaces, confusing the X-ray picture, as can be seen in Fig. 8. Again, when the ventricle is opened

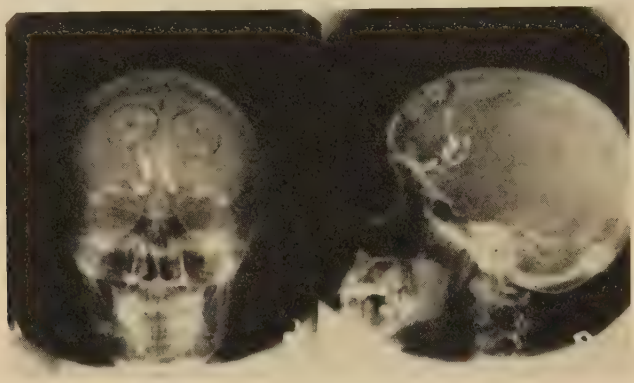

FIG. 12.—Gelatin-lipiodol. Bilateral undercutting of areas 32 and 12. Clips on cortical opening. (Obsessive neurosis.)

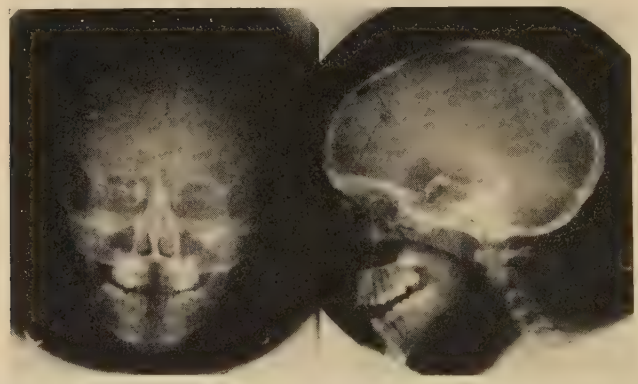

FIG. 13.—Gelatin-lipiodol. Resection of left amygdaloid nucleus. Clips on tip of temporal horn. (Epilepsy, violence.)

into, it may flow posterior to the limits of the lesion. Then it is not easy to be certain that the lipiodol goes into the whole area of leucotomy, even only approximately. The last objection is the degree of tissue reaction to lipiodol, with formation of cysts and tough scars, the role of which in causing mental changes is difficult to assess. We have observed this reaction several times in the course of reinterventions, and do not use free fluid lipiodol any more.

In the last few months we have used consistently a new material for X-ray studies—*gelfoam impregnated with lipiodol* (Le Beau and Pecker, 1950*b*). During the operation itself gelfoam bands are soaked in lipiodol, then carefully dried.

Under direct visual control the now opaque gelfoam is placed either on the surface of a topectomy or at the limits of a leucotomy. Ordinary gelfoam covers it to prevent its displacement. This technique has the advantage of showing very precisely the limits of the operation without escape of free drops of lipiodol, and of securing very good haemostasis. This material is absorbed —gelfoam and its included lipiodol—within weeks when placed on the cortex, somewhat later when in the white substance. Some typical examples of prefrontal operations thus defined are shown in Figs. 9, 10, 11 and 12. A new operation, on the amygdaloid nucleus in the temporal lobe, is seen in Fig. 13.

When in possession of satisfactory post-operative X-ray pictures it is simple enough to start measuring the lower and upper limits of the resected areas, from the foramen caecum as landmark. To make the numerals correspond with those in Brodmann's chart, a correction for perspective has to be made. Of course, we cannot hope to obtain absolute precision, and all our numerals may be $\pm \frac{1}{2}$ cm. wrong. Some specially doubtful estimates are allotted a question mark in the tables which follow (mostly it is the superior limit which is unreliable in these, the early cases).

In order to present our results more clearly, we shall group them in diagrams similar to the one used by Meyer and his co-workers (Beck, McLardy and Meyer, 1950). We are only concerned here with 56 cortical undercuttings and topectomies likely to include the whole or some part of area 10.* There is, of course, no justification for including our 4 topectomies of areas 46 and 45 and our 20 topectomies of areas 24 and 32.

Results and Discussion of Radiological Studies.

In the two tables published here the length of resection as evaluated radiologically is the only factor we take into consideration. The actual total surface area of resected cortex would, of course, be the best variable to employ, but we cannot imagine any practical means of measuring even roughly the extent of resected surface, due to the extreme variations in the depth of sulci. The width and depth of the resected blocks are approximately equal in most of our specimens, that is to say, 2·5 cm. by 1·5 cm.

The weight of the specimen might seem a good and significant variable. As a matter of fact we do not think so, for it is difficult to obtain comparable specimens because of their different amounts of blood content. Often the proportion of white and grey matter is quite different from one specimen to another, and leaves very little significance to the evaluation of total weights. Anyway, a few measurements of weights permit at least one negative statement : they do not militate in favour of an absolute quantitative theory of prefrontal lobe function ; for instance, in Table I (intractable pain), in two cases of unilateral topectomy of the same region, one good result was achieved with a 10-gm. resection, while a 19-gm. resection was a failure ; in two comparable cases of bilateral topectomy an 18-gm. resection succeeded, while one of 27 gm. was a failure. However, a more positive conclusion may be put forward tentatively : in a definite psychosis the resection of at least 20–25 gm.

* Fifty-two personal cases.

on each side seems necessary, as Pool showed, while in most of our cases of intractable pain and of simple neurosis it seemed to us that 10–12 gm. on each side was the minimum effective amount (Le Beau, 1950).

It seems, therefore, that the length of the specimen may be the only reliable variable. The four dotted horizontal lines in the Tables are the extreme lower and upper limits of area 10 (Meyer *et al.*) ; the line at 0 is the level of the foramen caecum.

(a) *Table I.*—Thirty-two cases of intractable pain. The left side of the table shows the resections in 23 successes, the right side those in 9 failures. Now this is a somewhat arbitrary division, because some of the successes were only important social improvements, and not all the failures were complete. The question of the duration of post-operative follow-up has also to be con-

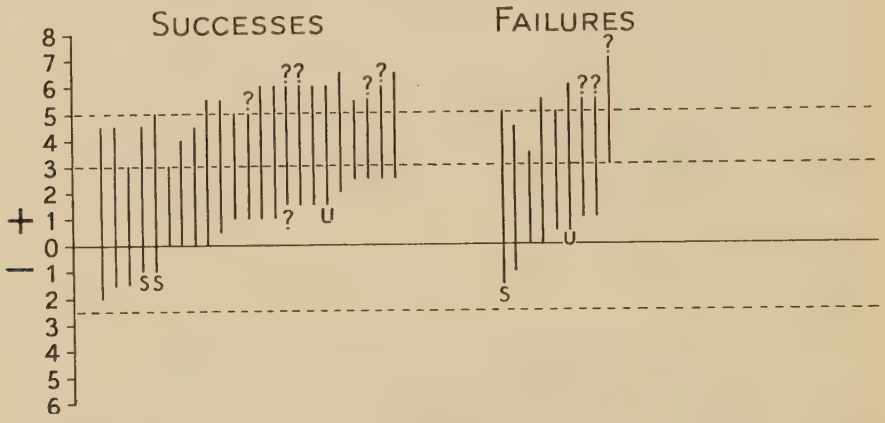

Table I.—Lengths of resections of 9 and 10 areas in 32 cases of instractable pain.

0 = level of foramen calcum.

The 0 and — 2–5 lines and the + 5 and + 3 lines, show the extremes of variation in lower and upper limits respectively of area 10, as measured by Meyer, Beck and McLardy in their preliminary series.

S = Cortical undercutting ; u = unilateral topectomy. All the other cases are bilateral topectomies.

sidered ; except for most of the cancer cases, this varies from four months to more than three years. Another difficulty is the allocation of a patient with phantom limb who was extremely well for four months, then a progressive and complete relapse occurred. Of course this case is not a clinical success, but it has been placed on the left side of the table because we believe that the topectomy had a physiological action (dramatic suppression of all drugs in this case of confirmed addiction).

Comparison of the two sides of Table I leads us to the following remarks :

The quantitative (length) factor is not all-important ; some short resections yield good results, while some long ones are ineffective.

The ablation of the major part of area 10 is not always enough to achieve good results, and the same can be said of the ablation of the junction of areas 9 and 10. This may seem a strong argument against the qualitative theory of prefrontal function. It should not be forgotten that we several times

performed resections of dysgranular, agranular or other granular areas (areas 32, 24, 46 and 45) in cases of intractable pain with consistent failure. In our opinion there is no doubt that a resection of the anterior part of area 9 and of area 10 is much more efficient than any other resection for intractable pain (Le Beau, 1950).

Incidentally, it should be remarked that none of the topectomies which for the sake of brevity we call "9 and 10" impinged upon the dysgranular region of the convexity (area 8), since this has never yet been found to extend lower than 7 cm. above the foramen caecum (Beck, McLardy and Meyer, 1950). Anyhow, it is more and more our tendency in intractable pain and anxiety cases to perform a resection of 4 or 5 cm. length and to cut at least as far ventrally as the foramen caecum.

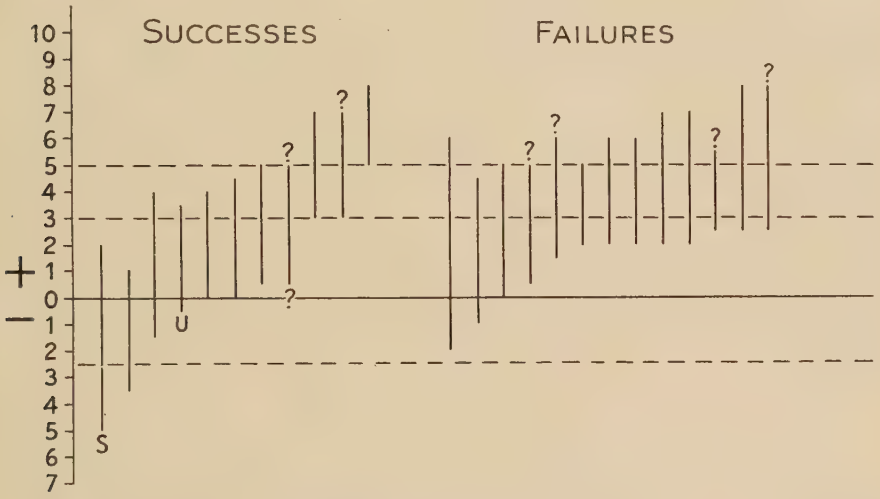

Table II.—Length of restrictions of 9 and 10 areas in different types of neurosis and psychosis (24 cases). Same Notation as in Table I.

It seems to us that an equally important conclusion is to be derived from the clinical comparison of surgically comparable cases belonging to both sides of Table I, and may be formulated thus : The ablation of most of the granular zone of frontal cortex is necessary for good results, but is not the only variable factor involved ; there are indubitably psychological factors in the mental pre-operative state of the patient which are of primary importance to the quality of the post-operative result. The presence of such a factor was already apparent in our first publications (Le Beau, 1948*b*), and it becomes more and more evident to us that a close psychological study will prove extremely valuable at least in the surgery of painful and neurotic states.

(*b*) A brief discussion of *Table II* is going to lead us to the same conclusions. The material comprises different kinds of illness : dementia praecox, schizophrenia, obsessive compulsive states, depressive states, and finally violent and agitated states mostly in epileptic patients—24 observations in all.

First of all the proportion of failures is here much larger and this does not surprise us, since we are dealing here with complex psychotic states in which,

even if one admits the qualitative theory, many different areas would have to be resected. In other cases, like the obsessive compulsive and the states of violence and agitation, we found that topectomy of areas 24 and 32 is much more efficient than of " 9 and 10 " (Le Beau and Pecker, 1950*a*).

Thus in our table there is no clear quantitative factor related to the quality of results. We are left, therefore, with the same need of a search for psychological factors to explain fully the post-operative results in these different kinds of mental disorders.

Fortunately modern psychology gives us more precise methods than before in the evaluation of pre-operative mentality. Halstead's (1949) work in the intellectual field is an important achievement. We believe that in prefrontal surgery the psychometrical study of temperament and character will prove more fruitful. In that respect the studies of Eysenck (1948) are extremely promising, and some very accurate work along these lines has already been published by Petrie (1949) on patients submitted to either lobotomy. There is little doubt that similar studies on topectomized patients will be instructive. For the time being we ourselves have to be satisfied with clinical impressions. We are well aware of their subjectivity; nevertheless we believe they can be a helpful guide in choosing the type of selective prefrontal operation, before and after which psychological variations will be measured. Also we think that material like ours, mostly composed of patients with intractable pain or relatively simple neurosis, is more likely to yield clear results than the complex psychotic patients who constitute the majority of cases in many psychosurgical statistics.

Concluding Remarks.

(1) We believe that topectomy is the surgical method which lends itself to the most scientific evaluation of the brain lesions in relation to the mental changes. In elderly patients with vascular disorders selective leucotomy should, however, be preferred. It should be borne in mind that one cannot avoid passing through area 10 when undercutting the orbital and mesial surface of the frontal lobe.

(2) In our series of 100 cases we had several post-operative deaths. These operative fatalities are, we believe, indirect proof of the frequent occurrence of minor complications responsible for mental effects.

Operations.	Cases.	Deaths.
Topectomies :	76	6
9–10 : intractable pain . . .	35	4
,, : other states	17	1
24–32	20	1
45–46	4	—
Cortical undercuttings	11	—
Lobotomies	13	2
	100	8

It should be noted that, due to a better choice of the different techniques, there was only one post-operative death among the last fifty cases.

(3) For the time being we can only sum up the following impressions suggested by a careful pre- and post-operative "practical" study of the patients, already published elsewhere in detail (Le Beau, 1950; Le Beau and Pecker, 1950*a*; Mahoudeau, Le Beau and Lemperiere, 1949).

(*a*) Ablation of granular cortex (areas 10 and adjacent parts of areas 9, 11 and 46) gives the best results in anxiety, depressive states and intractable pain. Results are better in neurotic than in psychotic states.

(*b*) Ablation of dysgranular and agranular cortex on the mesial side (areas 32 and 24) gives the best results in states of agitation and violence, especially in epileptics.

(*c*) A partial combination of (*a*) and (*b*), namely, cortical undercutting of the mesial side (i.e., part of areas 9 and 10, and areas 32 and 24), gives good results in obsessive compulsive states.

(*d*) We cannot say yet anything definite about orbital resections, nor about resections of the external aspect (areas 45 and 46), though it is our impression that the latter creates some intellectual and sphincteric disorders.

Summary.

The surgical factors of error are described in prefrontal psycho-surgery. General factors such as old age and vascular fragility are very important. During the handling of the brain extensive damage may cause venous and arterial interruption. In many operations there is a possibility of indirect diencephalic damage, topectomy being the safest operation in that respect. Results of post-operative radiological evaluation of topectomy are presented and discussed.

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PHENYLPYRUVIC OLIGOPHRENIA.

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"The study of phenylpyruvic amentia may throw light on the whole problem of mental deficiency."—Jervis.

Phenylpyruvic oligophrenia is a syndrome in which mental deficiency is accompanied by the excretion of phenylpyruvic acid in the urine.

It was first described by Föllings (1934), who made observations on 10 cases discovered in a survey of 430 mental defectives in Norway. In the next year Penrose described 2 cases in England (Penrose, 1935*a*). Jervis (1939) discovered as many as 200 cases in a large-scale survey of the 20,300 inmates of fourteen State Institutions in America. In Switzerland, Brugger (1942) found 2 cases and Morel (1944) found a third. In France, Rhein and Stoeber (1936) discovered 7 cases, and Turpin and Duchene (1945) discovered one certain case and one possible case which circumstances did not permit them to examine. In subsequent years numerous authors have written upon the subject of phenylpyruvic oligophrenia.

The syndrome was originally denoted by Föllings (1934) as imbecilitas phenylpyrouvica. Jervis (1937*b*) suggested the name phenylpyruvic oligophrenia. This is a good term, since patients suffering from the disease have been found in all grades of mental deficiency; moreover, it incorporates both the aspects of biochemical error and mental defect, which are essential components of the syndrome. Penrose referred to the condition as phenylpyruvic amentia in his first two papers on the subject (Penrose, 1935*a* and *b*), but later used the name phenylketonuria, which emphasizes the biochemical nature of the abnormality and brings the nomenclature into line with that of other comparable abnormalities, such as alkaptonuria and cystinuria.

Incidence.

Jervis (1939) estimated the incidence of phenylpyruvic oligophrenia as being from 3·0 to 0·5 per cent. of mental defectives. Brugger (1942) made a survey of 1,634 mental defectives in Switzerland and found the positive colour reaction given in phenylpyruvic oligophrenia in only 2 cases. Munro (1947) found 30 phenylpyruvic oligophrenics among 2,457 institutional idiots and imbeciles in Britain. He estimated, basing his calculation on the assumption that the incidence of imbeciles and idiots in the general population is 0·17 per cent., that the incidence of phenylpyruvic oligophrenia in the general population would be approximately 4 per 100,000; and on a basis of 40 million population, that there should be about 1,600 cases of the condition in Britain.

The present writer made a survey at the Fountain Hospital, London, of 553 mental defectives of all grades, consisting of females of all ages and males up to the age of 15 years. Fifteen cases of phenylpyruvic oligophrenia were discovered. An investigation into the family histories of the patients led to

the discovery of 2 more patients in other institutions suffering from the disease.

As regards sex distribution, Jervis, in 1937, stated that the excess of female over male cases seemed well established; 30 of his series of 50 cases of phenylpyruvic oligophrenia were female (Jervis, 1937*b*). Penrose (1949) stated that phenylketonuria has been ascertained more frequently in males than in females, his observation being based on data obtained in the intervening years since the statement made by Jervis. He suggests that this sex distribution may arise simply because females are healthier and live longer than males. Of the 15 cases of phenylpyruvic oligophrenia at the Fountain Hospital, 10 are female. In this instance the preponderance of females may be explained by the fact that there are females of all ages in the Fountain Hospital, whereas there are no males over the age of 15 years. No female patients over the age of 21 years at the Fountain Hospital were, however, found to be phenylketonuric.

Mental Level.

Jervis (1937*b*), using Stanford-Binet tests, gave the distribution of intelligence quotients for 45 cases as being 71 per cent. idiots with an intelligence quotient below 20, and 29 per cent. imbeciles with an intelligence quotient between 20 and 50. Penrose (1946) gives the distribution of cases on the scale of mental level as being some 60 per cent. of idiot grade, 30 per cent. imbeciles, and 10 per cent. of higher grade.

Of the 15 phenylpyruvic oligophrenics of the present series, 12 are idiots, 2 are imbeciles and 1 is of remarkably high intelligence in view of his condition, being in the dull-and-backward range. The percentage of idiots in the present series of cases is therefore high, being 80 per cent.

Clinical Picture.

The clinical features of phenylpyruvic oligophrenia are usually well marked.

The patient is in nearly every case fair-haired and fair-skinned, with light blue eyes. The exhibition of dilution of hair colour in phenylpyruvic oligophrenia in comparison with siblings and other members of the family is well illustrated by the case of Turpin *et al.* (1945), in which the patient was strikingly blond, although occurring in a family of darkly-pigmented people of Spanish descent. Jervis (1937*b*) quotes a similar case of an ash-blonde phenylketonuric patient in a Sicilian family, where all the other members for several generations were dark-haired.

The skin is soft, smooth and fine in texture. Bates (1938) observes the tendency towards marked dermatographia. Föllings (1934) and Jervis (1937*b*) remark upon frequent occurrence of eczema amongst the patients, and Penrose (1946) states that the skin, which may show pigmented patches, is unduly subject to dermatitis, and that hyperidrosis is commonly a feature. There is frequently cyanosis of the hands and feet, due to poor peripheral circulation.

The general physical development is symmetrical and harmonious. Föllings (1934) states that the majority of his first 10 cases had remarkably broad shoulders. Jervis (1937*b*) obtained anthropometric details from 18 patients,

in which only the craniometric data showed deviation from normal, the patients being considered as slightly microcephalic. Penrose (1946) and Frazier (1947) remark upon dwarfing of stature. Penrose (1946) remarks upon the reduction of head measurement as compared with normal. The stance is typical in the majority of cases, the patient standing with hips and knees flexed, in an attitude described by Delay *et al.* (1948) as " pithecoid."

The gait is stiff, short-stepped and on a broad base, with decreased associated movements. Frazier (1947) describes occasional retro- and anteropulsion. Kyphosis is described as being a common feature by nearly all writers, although Lepow (1944) considers this as secondary to the stooping posture.

Phenylpyruvic oligophrenics are usually free from gross physical deformities. Penrose (1935*a*) describes partial syndactyly in one case between the second and third toes. He also mentions that the incisor teeth are characteristically widely spaced (Penrose, 1946). Larcomb (1939) reported that congenital deafness had not been found in cases of phenylpyruvic oligophrenia, nor has it been reported since.

Bates (1938) described retinoscopy in 3 cases. He mentions a poor choriocapillaris, small vessels and a pale optic nerve. One case showed peripheral arrangement of pigment in an irregular fashion.

Hypertonicity of the limbs is a feature. Jervis (1937*b*) detected an increase in muscular tone in 70 per cent. of his cases and at times obtained cogwheel movements by passive movement of the upper extremities.

The reflexes are very brisk. Penrose (1946) maintains that all reflexes are accentuated, whilst Frazier (1947) describes increased response in the deep reflexes only. These signs have been interpreted by most authors as being referable to the extrapyramidal system. Delay *et al.* (1947) state that there is never a positive Babinski response.

Epileptic fits were observed by Jervis (1937*b*) in 21 per cent. of cases. Penrose (1946) states that these occur in the early years of patients who are severely mentally affected, and he has not known them to occur in phenylpyruvic oligophrenics over the age of ten years.

The patients tend to be hyperkinetic and to show stereotyped digital mannerisms (Penrose, 1946). These are especially a feature in patients of idiot grade. They may be pill-rolling or flicking in character, and are often intricate but performed rapidly and delicately. Such mannerisms in phenylpyruvic oligophrenics are described in detail by Delay *et al.* (1948) and are mentioned by Penrose (1946), Frazier (1947) and Jervis (1937*b*).

Delay and his co-workers (1947) concluded that on the whole patients with phenylpyruvic oligophrenia are apathetic and even stuporose, and frequently show echolalia and echopraxia. Penrose (1949) observes that sometimes isolated symptoms that form part of the characteristic picture of schizophrenia are seen in phenylketonuric patients. These symptoms include catatonia, outbursts of violence and stereotypy. Penrose points out that their psychiatric significance is difficult to determine ; they may be signs of psychosis, but alternatively may merely represent modes of reaction of an infantile nature ; implying that instinctual and emotional development has been retarded along with intellectual development.

Detection of Phenylpyruvic Acid in the Urine.

Föllings originally discovered the condition of phenylpyruvic oligophrenia by adding a 5 per cent. solution of ferric chloride to the urine. Where phenylpyruvic acid is present a characteristic olive green coloration is produced which develops several seconds after the addition of the ferric chloride solution, quickly reaches a maximum intensity, and fades in 15 minutes to half an hour. This test was used by the present writer in the survey of the 553 patients at the Fountain Hospital.

Penrose (1946) suggests neutralization of alkaline urine with dilute sulphuric acid before the test, and the present writer used 2 per cent. sulphuric acid, and on other occasions 2 per cent. acetic acid, for this purpose.

Several confirmatory tests have been devised to demonstrate the presence of phenylpyruvic acid in urine. Delay *et al.* (1946) describe the development of an intense green coloration on the addition of ammoniacal ferric alum to the urine. This is the basis of a method for the quantitative estimation of phenylpyruvic acid described by Polonowski *et al.* (1947). Delay *et al.* (1946) also describe a test where the development of an orange coloration occurs when picric acid is added to the alkalinized urine. Penrose and Quastel (1937) describe the preparation of the dinitrophenylhydrazone of phenylpyruvic acid. This is the basis of their method for the quantitative estimation of phenylpyruvic acid in urine.

Summary of Findings in the Present Series of Cases.

Fourteen of the patients in the present series each showed a number of the characteristics described by previous writers as being typical in phenylpyruvic oligophrenia.

The most common of these characteristics, seen in all 15 of the patients of the present series, was the wide spacing of the incisor teeth. In 10 cases the superficial and deep reflexes were very brisk. Nine were subject to eczema and dermatitis. Eight showed evidence of a poor peripheral circulation. Eight had slightly reduced head measurements as compared with normal (see Table I).

In six cases there was a history of epilepsy. Six were kyphotic. Five walked in the manner described by previous writers as being typical in phenylpyruvic oligophrenia, with short, quick steps on a broad base, with decreased associated movements. Four showed the " pithecoid " stance with flexion at knees and hips. Four had stereotyped digital mannerisms. Three had minor pigmentary anomalies, consisting in two cases of pigmented moles and in the third of a " café au lait " birthmark. In three, thinning of the retinal pigmentation was observed, but this was within normal limits for children as blond as the patients in which it occurred. Hyperidrosis was observed in only two patients, and dermatographia was seen in only two.

Although it has been stated that a positive Babinski response is never found in phenylpyruvic oligophrenia, (Delay *et al.*, 1947), the plantar responses were plantar-extensor in three cases ; each of these patients was subject to epilepsy.

TABLE I.

Patient	Age (years).	Sex.	Head circumference in inches.
Pauline P—	4 +	Female	19·0
Francis W—	6 +	Male	20·2
Carol B—	6 +	Female	18·7
Frances T—	7 +	Female	19·0
John R—	7 +	Male	21·0
Georgina H—	8 +	Female	19·7
Brian C—	8 +	Male	20·2
Margaret W—	9 +	Female	21·0
Alan J—	9 +	Male	20·2
Arthur P—	12 +	Male	20·7
Iris S—	12 +	Female	20·0
Derek T—	14 +	Male	21·5
Lilian B—	18 +	Female	19·0
Pamela P—	20 +	,,	21·0
Joan S—	21 +	,,	20·0

In addition to the characteristics that have been described as typical in phenylpyruvic oligophrenia by former authors, the present writer has observed others occurring with frequency. Twelve of her patients had pes planus, which was usually very severe ; in some cases the patient bearing weight on the inner borders of the feet and walking with the soles everted. The 12 patients in which this was observed comprised all those of the series who were able to stand and walk.

In 5 of the patients there was a wide gap between the first and second toes. On close inspection, in each of these patients there was a very mild degree of syndactyly between the roots of the second and third toes, which probably caused the second toe to be drawn laterally, thus widening the first interdigital cleft. Penrose (1935*a*) mentions partial syndactyly between the second and third toes in a phenylpyruvic oligophrenic patient, but does not describe a widening of the first interdigital cleft.

In 10 of the patients the upper jaw was prominent and had the appearance of overhanging the lower jaw, and caused the teeth to protrude. The present writer believes that this expansion and prognathos of the maxilla is the factor causing the wide-spacing of the incisor teeth in patients suffering from phenylpyruvic oligophrenia.

In one patient a palpable and slightly enlarged liver was observed.

Fourteen of the patients in the present series were fair-skinned. Their irides were light in colour. Their hair was either red or fair, the darkest hair being medium brown in colour. The hair-colour of the patients and that of their parents and siblings was analysed by means of spectrophotometry and a relative dilution of hair colour in the case of the patients in comparison with that of the other members of their families was consistently demonstrable (Penrose and Cowie, 1951).

The fifteenth patient, John R—, however, had dark brown hair and olive skin,

and his irides were almost black. Moreover, the only characteristic he possessed beside the excretion of phenylpyruvic acid, described by former writers as being typical in phenylpyruvic oligophrenia, was wide-spacing of the incisors. His level of intelligence was in the dull-and-backward grade, and on the basis of this finding alone his case is unique, since no other case of phenylpyruvic oligophrenia has been reported in which the level of intelligence, as revealed by psychometry, has been so high (Cowie, 1951). His output of phenylpyruvic acid was low, being only half a gramme daily. The usual finding is that approximately 1 gm. of phenylpyruvic acid is excreted daily in urine by phenylketonuric patients (Penrose, 1946), and the findings of the present writer, who carried out quantitative estimations on the urine of all 15 patients in her series, are in accordance with this average figure.

Table IV shows the distribution of the characteristic features found in the 15 cases of the series.

The Genetics of Phenylpyruvic Oligophrenia.

The high familial incidence of phenylpyruvic oligophrenia, i.e. its occurrence in sibs of the same fraternity, points to the probability of a genetic mechanism.

Penrose (1935*b*) made the first publication concerned with the inheritance of phenylpyruvic amentia. In this paper he gave a pedigree consisting of five generations, demonstrating the mode of action of a rare recessive gene in a consanguineous family. This gene, he postulated, was responsible for the appearance of phenylketonuria in the family. In the same paper, Penrose advanced the hypothesis that the gene for phenylketonuria is not completely recessive, but that it exerts an influence upon the heterozygotes, predisposing them to mental breakdown. The heterozygotes in the family concerned showed a marked tendency to develop insanity at the involutional period of life.

Jervis (1937), in his introductory study of 50 cases of phenylpyruvic oligophrenia, made a critical examination of the anamnestic data, and concluded that such exogenous agencies as maternal health, birth trauma, syphilis, infectious disease or endocrine disturbance could be excluded as aetiological factors in the production of phenylpyruvic oligophrenia. He pointed out, moreover, that the family incidence of the condition suggested that a genetic mechanism is of significance, and subsequent statistical elaboration and critical analysis of the figures provided by his material afforded justification for regarding the condition as determined by a single recessive gene.

A later paper by Jervis (1939) was devoted to the study of the influence of heredity on phenylpyruvic oligophrenia. His material consisted of 200 patients grouped in 125 families, and he showed that factual data proved that the conditions ran in families. Many environmental factors were considered, and the conclusion was reached that without exception the data indicated the improbability that factors due to the external environment play a significant role in the causation of the disease. Various genetic possibilities for the production of phenylpyruvic oligophrenia were then considered, including the action of a single dominant gene, of two complementary dominant genes, of sex-linked genes and of a recessive autosomal gene. In connection with the latter, the ratios of affected to normal children, the rate of consanguinity among

parents and the distribution of the condition among ascendant and collateral relatives of affected individuals were all studied. The findings were all consistent with the quantitative requirements of the theory of monomeric recessivity, and indicated that the disease is determined by an autosomal recessive gene.

To these considerations a suggestion for practical application was added; the parents of affected children should be discouraged from having other children, since, according to the laws of inheritance, one-quarter of these would be affected, and one-half would be carriers, and consanguineous marriages amongst members of affected families should be particularly avoided.

As the gene producing phenylpyruvic oligophrenia is rare and recessive, the incidence of consanguinity in families where the condition is found might be expected to be high, especially in regions such as Switzerland, where only three cases have been reported, two by Brugger (1942) and one by Morel (1944). Morel traced the pedigree of his case back to the year 1660 to show there was no consanguinity. Pichot, Delay and Bertagna (1944) also traced the genealogical tree of their patient back to 1780 over seven generations, to exclude the incidence of consanguinity. In the 125 families in the series of Jervis (1939) the parents of only 7 families were cousins. In the case described by Delay, Pichot, Desgrez and Delbarre (1946) the father and mother were first cousins. Munro (1947) estimates the incidence of parental consanguinity in phenylpyruvic oligophrenia as being approximately 10 per cent., using a method of calculation depending upon the concept of gene frequency in the population.

Examination of data relating to the family histories of the 15 patients of the present series reveals evidence supporting the belief that the condition is due to a recessive gene. There is no consanguinity of the parents of any of the patients. In 9 cases the urine of both parents, and in 1 case the urine of the widowed mother, was tested and found to contain no phenylpyruvic acid, nor did these parents show any signs of mental deficiency. The remaining three pairs of parents could not be traced at the time this work was being carried out, but family histories taken previously state that none of these parents was mentally deficient.

Familial incidence is shown in the present series. In two of the families concerned there are a brother and a sister, both affected, with no normal siblings.

In the sibship of which the phenylketonuric patient Derek T— is a member, it has been confirmed that at least one other sibling suffers from phenylpyruvic oligophrenia, and it is believed to be very likely that a third sibling, now dead, was also phenylketonuric. There are 5 normal siblings in the sibship.

Another family, of whom Carol B— is a member, is of interest. The brother of the patient's father is also phenylketonuric. If the theory of inheritance by a recessive gene is accepted, then both of the paternal grandparents as well as both of the parents of Carol B— must have been heterozygotes for phenylpyruvic oligophrenia.

In the case of only one parent in the group is there evidence of any mental disturbance. This parent is a highly distractable and excitable individual of manic-depressive type, but he has not yet shown true insanity or mental

breakdown, which tend to appear in heterozygotes according to Penrose (1935*b*). He has not, however, yet reached the involutional period of life in which mental breakdown is most likely to occur according to the observations of Penrose.

Genetic Linkages.

Phenylpyruvic oligophrenia is a clear-cut biological condition, and such a sharply segregated characteristic, not very common in human biology, facilitates genetical studies. Penrose (1941) pointed out that the material provided by cases of phenylpyruvic oligophrenia is particularly suitable for use in the search for possible linkages on the autosomal part of the human chromosome map.

Munro, Penrose and Taylor (1939) collected data concerning 25 families in England, and observed that there was a suggestion of genetic linkage between the ABO blood agglutinogen allelomorph series and the gene for phenylpyruvic oligophrenia, but the scarcity of material permitted only tentative conclusions to be drawn. Penrose (1941) put on record data obtained from a Canadian family in which there were two phenylketonuric patients. Further data are provided by Penrose (1945), who studied ABO groupings of another Canadian family, and by Munro (1947) who obtained material including ABO and MN blood groupings from families in which there is phenylpyruvic oligophrenia. The statistical significance of the suggestion of linkage is doubtful where there is yet a relatively small number of families. Penrose (1945) points out that should further investigation continue to support the suggestion of linkage between phenylpyruvic oligophrenia and the ABO agglutinogens, the result will be of great theoretical interest although the linkage is not close enough to enable the blood types by themselves to be used as markers in identifying carriers of the condition.

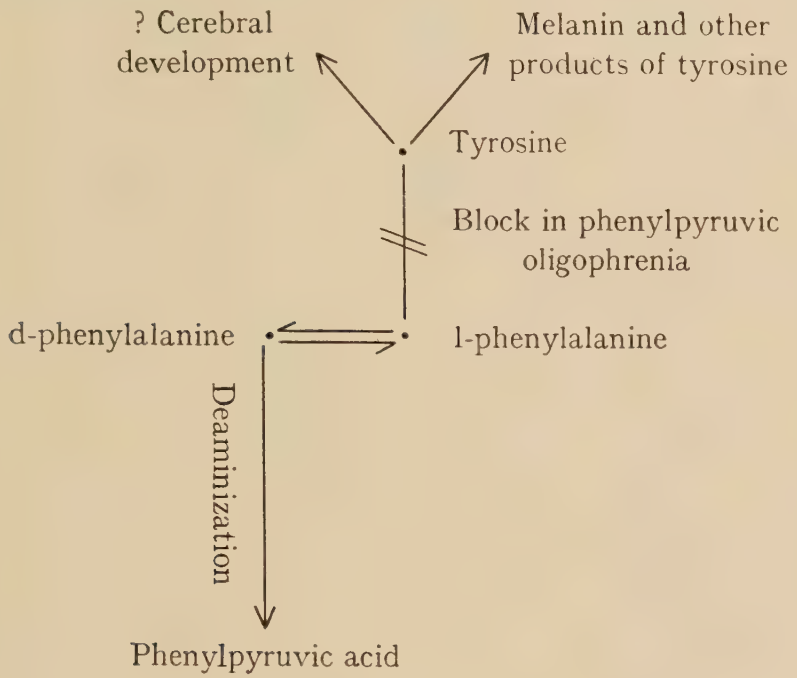
Study of the blood grouping was made in 8 of the families of which patients in the present series were members. Besides the ABO and MN groups, S, P, Lewis, Kell, Lutheran and Rhesus groupings were studied, and in one family the Duffy grouping was used. The findings are given in Table II. In Families 2, 5 and 7, where there are two affected siblings in each sibship, there is no evidence against linkage between phenylpyruvic oligophrenia and the ABO, MN, S, Lewis and Lutheran agglutinogens. In Family 7 the differences in the Rhesus, P, and Kell groupings of the phenylketonuric siblings, suggest that there is no genetic linkage between these agglutinogens and phenylpyruvic oligophrenia.

The Biochemistry of Phenylpyruvic Oligophrenia.

The fundamental biochemical error in phenylpyruvic oligophrenia is a disturbance in the metabolism of phenylalanine.

It is believed that in the normal individual, phenylalanine, in the laevo form, is converted to tyrosine, but that there is a block in this process in the phenylketonuric patient. In him, phenylalanine in the dextro form is deaminized, presumably in the kidney, to phenylpyruvic acid, which is excreted in the urine.

The biochemical picture in phenylpyruvic oligophrenia may thus be shown diagrammatically as follows :



Experimental evidence of many workers throws light on the metabolism of phenylalanine in the normal individual and in the phenylketonuric patient.

In Dakin's classical experiment it was shown that *in vitro* phenylalanine is converted to phenylpyruvic acid in the presence of kidney slices. Upon this evidence he based his hypothesis that the normal pathway of metabolism of phenylalanine passed through phenylpyruvic acid, the conversion being effected by oxidative deaminization.

Embden and Baldes (1913) put forward the hypothesis that the normal pathway of catabolism of phenylalanine was through tyrosine, the first step being a nuclear oxidation in the para position. This was supported by the fact that perfusion of the liver with dl-phenylalanine led to the production of tyrosine.

Föllings (1934) originally suggested that two biochemical lesions may exist in phenylpyruvic oligophrenia ; first, a pathological oxidative deaminization, transforming phenylalanine to phenylpyruvic acid, occurring only in the phenylketonuric individual ; and, secondly, a disturbance in the breakdown of the phenylpyruvic acid thus formed, since in the normal individual ingestion of this acid leads to rapid breakdown rather than to urinary excretion. Experiments carried out by Penrose and Quastel (1937) in which phenylpyruvic acid was fed to both phenylketonuric patients and to normal individuals, supported this belief that phenylpyruvic acid is metabolized with greater difficulty in the phenylketonuric patient than in the normal subject.

TABLE II.

Family.	Member.	ABO.	MN.	S.	Rh.	P.	K.	Le.	Lu.	Fy.
1	Father	A_2	N	+	rr	+	–	–	–	..
	Mother	A_1	MM	–	rr	+	–	–	–	..
	Patient, J. S—	A_1	MN	+	rr	+	–	–	–	..
	Sister	A_1	MN	–	rr	+	–	–	–	..
2	Father	O	MN	+	R_1R^1	+	–	–	–	..
	Mother	O	M	+	rr	+	–	–	–	..
	Sister, H. F—	O	MN	+	R_1r	+	–	–	–	..
	Sister, J. T—	O	MN	+	R^1r	+	–	–	–	..
	Patient, L. T—	O	MN	+	R^1r	+	–	–	–	..
	Sister, Jo. T—	O	MN	+	R_1r	+	–	–	–	..
	Patient, D. T—	O	MN	+	rr	+	–	–	–	..
	Sister, P. T—	O	M	+	R_1r	+	–	–	–	..
3	Mother	A_1	NN	+	R_1R_2	+	–	+	–	..
	Patient, G. H—	A_1	NN	+	R_1R_2	+	–	–	–	..
	Sister	A_1	NN	+	R_1R_2	+	–	–	–	..
4	Father	O	MN	–	$R_1{}^wR_1$	+	–	–	–	..
	Mother	B	MM	+	R_1r	–	–	–	–	..
	Brother, P. C—	O	MN	–	$R_1{}^wR_1$	+	–	–	–	..
	Sister, P. C—	O	MN	–	$R_1{}^wR_1$	+	–	–	–	..
	Patient, B. C—	O	MM	–	$R_1{}^wr$	+	–	–	–	..
	Brother, A. C—	O	MN	–	R_1r	+	–	–	–	..
	Brother, C. C—	B	M	+	$R_1{}^wR_1$	+	–	–	–	..
5	Father	O	NN	–	rr	–	–	–	–	..
	Mother	B	NN	–	rr	–	–	–	–	..
	Patient, P. P—	O	NN	–	rr	–	–	–	–	..
	Patient, A. P—	O	NN	–	rr	–	–	–	–	..
6	Father	BO	M	+	R_1r	+	–	..	–	–
	Mother	A_1B	N	–	rr	+	–	..	–	+
	Sister, S. J—	A_1O	MN	–	R_1r	+	–	..	–	+
	Patient, A. J—	A_1B	MN	–	R_1r	+	–	..	–	+
	Brother, D. J—	A_1O	MN	–	rr	+	–	..	–	+
	Brother, B. J—	B	MN	–	R_1r	+	..	..	–	..
7	Father	A_1B	N	–	R_1r	–	+	..	–	..
	Mother	A_1B	N	–	R_1R_1	+	–	..	–	..
	Patient, M. W—	A_1B	N	–	R_1r	–	+	–	–	..
	Patient, F. W—	A_1B	N	–	R_1R_1	+	–	–	–	..
8	Mother	O	MN	+	R_2	+	–	..	–	..
	Sister	A_1	MN	+	R_2	+	–	..	–	..
	Patient, J. R—	A_1	MN	+	R_2r	–	–	+	–	..

Penrose and Quastel (1937) also studied the effects of feeding phenylalanine to phenylketonuric and to non-phenylketonuric individuals. They found that in phenylpyruvic oligophrenia only part of the phenylalanine ingested appears as phenylpyruvic acid. They showed also that the phenylketonuric patient has almost as great difficulty in metabolizing l-phenylalanine as d-phenylalanine. The non-phenylketonuric subject, on the other hand, apparently metabolizes l-phenylalanine with greater ease than either the racemic or d-forms, and both optically active forms are metabolized less completely in the phenylketonuric patient than in the normal individual.

Penrose (1937) believed that phenylalanine catabolism could follow two pathways, the main pathway passing through phenylpyruvic acid, and a subsidiary pathway passing through tyrosine. Jervis and his co-workers (1940), after carrying out metabolic studies with phenylalanine, postulated that these two pathways were reversed in importance. They believed that the main pathway passed through tyrosine, and that the pathway of metabolism passing via phenylpyruvic acid was accessorial.

If one accepted the classical conception of Dakin that phenylalanine is

normally catabolized to phenylpyruvic acid, the disturbance in phenylpyruvic oligophrenia would seem to be a fault in the catabolism by which phenylpyruvic acid is disposed of in the body.

If one agreed with Embden and Baldes (1913) that phenylalanine is normally metabolized by way of tyrosine, phenylpyruvic acid would seem to be an abnormal metabolite produced by an abnormal method of metabolism, the transformation of phenylalanine to tyrosine being blocked. Further evidence of phenylalanine being metabolized to tyrosine and its derivatives was afforded by an observation by Medes (1932), who found that in a case of tyrosinosis the urinary output of Millon-reacting substances increased after the ingestion of phenylalanine.

New light was thrown on the problem when Jervis (1940) and his co-workers examined the blood and cerebrospinal fluid of phenylketonuric patients. Their findings excluded the presence of appreciable amounts of phenylpyruvic acid in these body fluids, although the phenylalanine content was high. It was on the basis of these findings that Jervis reversed his belief in the relative importance of the two possible pathways of metabolism of phenylalanine which he formerly held (Jervis, 1937). He now concluded that the essential biochemical characteristic of the disease consisted of an inability of phenylketonuric subjects to dispose of phenylalanine at a normal rate rather than in the failure to break down phenylpyruvic acid. He considered the presence of phenylpyruvic acid in the urine as an incidental phenomenon resulting from the deaminization of a portion of the blood-phenylalanine by kidney tissue. He considered the formation of phenylpyruvic acid in the kidney as representing an alternative pathway in the catabolism of phenylalanine, this route being available when the normal pathway is blocked. He now believed the normal route of phenylalanine catabolism to be through tyrosine, and not through phenylpyruvic acid. In support of this belief he gave evidence of studies in alcaptonuria, where it was shown that both phenylalanine and tyrosine caused an increase in the elimination of homogentisic acid; he quoted the experimental evidence of Embden and Baldes (1913), and of Medes (1932). He also described experiments with tissue slices indicating that phenylpyruvic acid fails to give acetoacetic acid under conditions in which phenylalanine and tyrosine yield this compound. Other evidence quoted of the close metabolic relationship between tyrosine and phenylalanine was provided by studies on experimental alcaptonuria, and by the finding of l-p-hydroxyphenyllactic acid in the urine of vitamin C deficient premature infants following the ingestion of either phenylalanine or tyrosine.

It is upon the conclusions drawn by Jervis and his co-workers (1940) from their fundamental experiments, that is based the conception now held of the biochemistry of phenylpyruvic oligophrenia as outlined above in diagrammatic form.

The relationship of the biochemical error in phenylpyruvic oligophrenia to mental deficiency is not yet fully understood, but one may conjecture that the deficiency of tyrosine or of its products or of the enzyme system required for the metabolism of phenylalanine to tyrosine may in some way impair cerebral development or function. On the other hand, the accumulation of excessive

phenylalanine in the tissues of phenylketonuric patients as demonstrated by Jervis and his co-workers (1940) may act as a toxic factor, inducing mental deficiency. To investigate the possible toxic effects of excessive phenylalanine it would be interesting to feed phenylketonuric patients with a diet entirely free from phenylalanine. This has, however, great practical difficulties. Alternatively, the feeding of massive doses of phenylalanine to experimental animals might throw light upon the matter, but again difficulties would arise in recognizing any signs appearing in an experimental animal comparable to those seen in phenylpyruvic oligophrenia in man.

The biochemical error seems compatible with the physical signs of lack of pigmentation of skin and irides and of dilution of hair-colour, if one accepts the deficiency of tyrosine available from phenylalanine in these patients, tyrosine being a precursor of the pigment melanin, although it must be borne in mind that tyrosine is available directly from the diet, and that the deficiency is therefore not a total one. This is supported by the evidence obtained by Block *et al.* (1940), who showed that the tyrosine contents of serum from phenylketonuric and from normal individuals were approximately the same, being 4·3 per cent. in the former and 4·1 per cent. in the latter.

There is no evidence at present against the possibility of an enzyme deficiency in phenylpyruvic oligophrenia, and Penrose (1949) postulates the lack of some enzyme capable of splitting and utilizing the laevo-phenylalanine. Himwich and Fazekas (1940) supposed that the low level of mental activity in patients suffering from phenylpyruvic oligophrenia might be attributed to diminished rate of oxidation. By examination of the blood from the internal carotid artery and internal jugular vein they established that there was a diminution in cerebral oxidation in patients suffering from phenylpyruvic oligophrenia. They stated that such a diminution may be due to the lack of oxidative enzyme, a defect similar to that which prevents the oxidation of phenylalanine. They also demonstrated, however, a similar diminution in the cerebral oxidation of mongols, and there is no evidence to prove that this phenomenon is not common in mental defectives generally.

Several authors have commented upon the possibility of enzyme deficiency in phenylpyruvic oligophrenia.

Pichot *et al.* (1947) postulated a possible disturbance in the enzymes in the kidney, since feeding with either dextro or laevo forms of phenylalanine leads to increased output of phenylpyruvic acid in the phenylketonuric patient, but phenylketonuria is stimulated only by ingestion of the dextro form in the normal individual.

Jervis (1937*b*) observed that there was excellent ground to assume that the oxidation of a single product of metabolism may be impaired without affecting the capacity of the body to oxidize other substances, since it appears that oxidizing agents bear a special relation to the substance undergoing change, and that such a specificity seems to exist for the catalysts involved in the oxidation of phenylalanine. In another paper Jervis (1937*a*) again asserts that it may be safely assumed that an enzyme deficiency is at fault in phenylpyruvic oligophrenia, stating that the nature of the enzyme system responsible for the breakdown of phenylalanine had been worked out by Bernstein.

Pichot, Delay and Bertagna (1949) carried out experiments to determine whether an enzyme, phenylalanine-oxidase, exists in the circulating blood, conjecturing that the congenital absence of such an enzyme could be the fundamental disturbance in phenylpyruvic oligophrenia. They studied the urinary elimination of phenylpyruvic acid in cases in which exsanguino-transfusions had been performed. The result was completely negative. The enzyme, however, may well exist in some other organ or tissue than the blood, although there is no report to date of further quest along these lines.

The present writer hopes that future liver-biopsy to be carried out upon the phenylketonuric patients of her series will provide material for an experiment on the following lines.

From the findings of Embden and Baldes (1913) it is assumed that conversion of phenylalanine to tyrosine can take place in the liver in the non-phenylketonuric individual. The liver tissue removed at biopsy from the phenylketonuric patients would be placed, immediately following removal, in a physiological solution containing phenylalanine. Liver tissue obtained from non-phenylketonuric individuals at biopsy would be treated in the same way. A study would be made of the behaviour of the liver tissue from the phenylketonuric and non-phenylketonuric subjects with respect to the production of tyrosine. Decreased production of tyrosine in the case of the liver obtained from the patients suffering from phenylpyruvic oligophrenia would point to the metabolic error being seated in the liver in this condition.

Blood Chemistry in Phenylpyruvic Oligophrenia.

Investigation into the blood chemistry of the patients of the present series was carried out. The results are given in Table III.

The increased reflexes and tendency towards hypertonicity often found in phenylpyruvic oligophrenia and seen in some of the present patients, suggested that these manifestations might have been due to a low level of serum calcium. Investigations showed, however, that this was not the case. The serum calcium and phosphorus levels were within normal limits in each of the 15 cases.

Table III.

Name.	Age.	Serum calcium mg.%	Serum Phosphorus mg. %.	Alkaline Phosphates K units.	Cholesterol. Total mg. %.	Free mg. %.	Ester mg. %.	Free/Ester.
ilian B—	18 yrs. 8 mths.	9·1	4·1	12	165	53	112	1/2·2
arol B—	6 ,, 9 ,,	9·3	4·7	13	196	50	146	1/2·9
rian C—	8 ,, 11 ,,	9·6	5·0	19	189	41	148	1/3·6
eorgina H—	8 ,, 4 ,,	9·7	4·5	13	177	41	136	1/3·3
lan J—	9 ,, 9 ,,	9·7	4·2	10·5	225	65	160	1/2·5
rthur P—	12 ,, 2 ,,	10·2	5·3	17·5	225	90	135	1/1·5
auline P—	4 ,, 6 ,,	10·1	5·3	13	225	65	160	1/2·5
amela P—	20 ,, 2 ,,	10·8	4·0	8·5	135	45	90	1/2·0
ohn R—	7 ,, 9 ,,	10·0	4·9	13	188	40	148	1/3·7
oan S—	21 ,, 9 ,,	9·4	3·6	9	200	51	149	1/2·9
ris S—	12 ,, 9 ,,	10·3	5·0	15·5	177	41	136	1/3·3
erek T—	14 ,, 10 ,,	10·6	4·9	22·7	142	35	107	1/3·0
rances T—	7 ,, 8 ,,	10·1	5·2	26	165	56	109	1/1·9
rancis W—	6 ,, 5 ,,	9·9	4·9	15	118	32	86	1/2·7
argaret W—	10 ,, 1 ,,	9·6	4·5	14	212	59	153	1/2·6

TABLE IV.

	Carol B—	Lillian B—	Brian C—	Georgina H—	Alan J—	Arthur P—	Pauline P—	Pamela P—	John R—	Iris S—	Joan S—	Derek T—	Frances T—	Francis W—	Margaret W—
Fair hair and fair skin	+	+	+	+	+	+	+	+	..	+	+	+	+	+	+
Blue irides	+	+	+	+	+	+	+	+	..	+	+	+	+	+	+
Widely-spaced incisors	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Brisk reflexes	+	+	..	+	+	..	..	+	..	+	+	+	..	+	+
Tendency to dermatitis	..	+	..	+	+	..	+	+	..	+	+	..	..	+	+
Poor peripheral circulation	+	+	+	+	..	..	+	..	..	..	..	..	+	+	+
History of epilepsy	+	..	..	+	..	..	+	..	..	..	+	+	..	..	+
Kyphosis	..	+	..	+	..	..	..	+	..	..	+	+	..	..	+
Characteristic gait	..	+	..	+	..	..	..	+	..	+	+	..	..	..	..
Pithecoid stance	..	+	..	+	..	..	..	+	..	..	+	..	..	..	..
Digital mannerisms	..	+	..	..	..	..	..	+	..	..	+	..	..	+	..
Pigmentary anomalies of skin	..	..	..	..	..	..	+	+	..	..	+	..	..	..	..
Thinning of retinal pigment	+	..	..	..	..	..	+	..	..	..	..	..	..	+	..
Dermatographia	..	..	..	..	..	..	+	..	..	..	..	+	..	..	..
Hyperidrosis	..	..	..	..	..	..	..	+	+	..	..	..	..	..	..
Pes planus	..	+	+	+	+	+	..	+	+	+	+	+	..	+	+
Partial syndactyly of toes	..	+	+	..	..	..	..	..	+	+	+	..	..	..	..
Prognathos of maxilla	..	+	+	+	+	+	+	+	..	+	+	+	..	..	..
Palpable liver	..	..	..	..	..	..	..	..	..	..	..	..	..	+	..
Idiot	+	+	+	+	+	..	+	+	..	+	+	..	+	+	+
Imbecile	..	..	..	..	..	+	..	..	..	..	..	+	..	..	..
Dull and backward	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..

Values for blood cholesterol were obtained, and in each case these were within normal limits. This provides additional evidence in favour of the belief that there is no dysfunction of the thyroid in phenylpyruvic oligophrenia.

THE PATHOLOGY OF PHENYLPYRUVIC OLIGOPHRENIA.

Until the time of writing, only two post-mortem examinations upon phenylpyruvic oligophrenics have been reported in publications, and a third post-mortem examination, the report of which has not yet been published, was performed at the Middlesex Colony in July, 1949. The writer was present at this event and observed the macroscopic appearances. The histological findings have not yet been made known.

The body was that of a small woman aged 25. The organs, including heart, liver, spleen and kidneys were all correspondingly small. The brain weighed $2\frac{1}{2}$ lb. and showed no macroscopic defect. There was a marked kyphosis and lumbar lordosis. The hair was slatey fair, and the irides were pale bluish-grey. The hands were in a "main en griffe" position, with hyperextension at the metacarpo-phalangeal joints, and it was stated that this was a characteristic of the patient during life. The liver lobules were well-defined on examination by the naked eye. The liver was leathery to feel. There was a small amount of pus in the upper calyx of the left kidney. When 5 per cent. ferric chloride solution was dropped onto the cut surface of the kidney the tubules gave a dark green coloration. No colour reaction was produced when ferric chloride solution was dropped on the cut surface of the liver or spleen. There were calcified lymph nodes in the mesentery. No abnormalities were

observed by the naked eye in the peripheral nerves. The macroscopic appearance of the thyroid was normal. The cause of death was established as pneumonia.

The patient was reported to have been of idiot grade, being unable to walk, bed-ridden, doubly incontinent and unable to speak or to do anything for herself. Her sister, who died as a child at the Fountain Hospital in 1925, was a fair-haired idiot with light grey eyes and widely-spaced incisor teeth. She died following an attack of jaundice. She was classified as an imbecile of no specific type, but was almost certainly suffering from phenylpyruvic oligophrenia. Apart from the case of her sister, whose post-mortem findings are described above, there was reported to be no case of mental deficiency or insanity in the family history, and the parents were not consanguineous.

The two post-mortem reports have been published by Penrose (1939) and by Coquet *et al.* (1944).

Penrose's case was that of a male idiot, aged 9 years and 7 months ; bronchopneumonia was found in both lungs. The most striking feature of the post-mortem examination was the finding of several tense swellings, up to 1 cm. in diameter on the trunks of both vagi, and smaller ones on nearly all their branches. The phrenic nerves, medial brachial cutaneous, ulnar, median, musculospiral and sciatic nerves were also affected, and there were multiple small nodules of a similar kind near the pudendal and coeliac plexuses. When cut through, some fluid could be expressed with difficulty from the swelling, but neither the nerve nor the fluid gave a colour with ferric chloride. Microscopically the appearances in sections of the sciatic nerve were indistinguishable from those found in some cases of neurofibromatosis, with a decreased amount of interstitial connective tissue and loss of myelin in many of the nerve fibres. The localized swellings appeared mainly due to presence of fluid which had infiltrated a network of nerve fibres. The brain was soft and oedematous, the nerve cells of the cortex being widely spaced and the connective tissue of the grey matter loosely packed. The liver was not studied. Penrose points out that the swellings on the nerves may be related to changes observed in progressive hypertrophic polyneuritis which have been attributed to the action of toxins, and suggests that the swellings and hypertrophy of peripheral nerves in this case may have been due to a toxic action of phenylpyruvic acid, and that the association between metabolic abnormality and cerebral oedema may have a parallel explanation.

In the post-mortem examination reported by Coquet *et al.* (1944), perilobular fatty degeneration was found in the liver, and there was stasis in the intra-trabecular capillaries. There was liquefaction of the pyramidal cells of the cerebral cortex in layers II, III and IV. There was a small zone of necrosis in the white matter of the frontal lobe. The interstitial tissue of the thyroid was said to be "rich in nuclei." No abnormality of the peripheral nerves was discovered.

In addition to the definite pathological evidence mentioned above, the post-mortem report is available of a female idiot, Gladys T—, who died at the Fountain Hospital in 1941, aged 18½. Her case has already been described, together with those of her brothers, Derek T— and Leslie T—, who are both

phenylketonuric. It is almost certain that Gladys T— herself suffered from phenylpyruvic oligophrenia. The patient was said to be very obese when she died. Patches of broncho-pneumonia were found in both lungs. Apart from this the only abnormal findings recorded were that the heart was flabby with infiltration of fat, and that the liver, weighing 3 lb. 3 oz. was enlarged and light-coloured, with infiltrated fat throughout. The brain showed no macroscopic abnormality and weighed 2 lb. 4 oz.

The Liver in Phenylpyruvic Oligophrenia.

There are certain indications that the liver may be the seat of the metabolic error in phenylpyruvic oligophrenia.

It has been shown that the fundamental biochemical disturbance underlying the condition is an inability of the patient to dispose of phenylalanine at a normal rate (Jervis, 1940). Jervis (1947) demonstrated an increase of a tyrosine-like substance in the blood of rabbits, following intravenous administration of phenylalanine. This indicated that the conversion of phenylalanine was not due to changes occurring in the intestinal tract. The experimental evidence of Embden and Baldes (1913), who found tyrosine in the perfusion fluid after perfusing the liver with phenylalanine, is in favour of the liver as being an organ in which the metabolism of phenylalanine takes place. Coquet, Myle *et al.* (1944) describe pathological changes in the liver in a post-mortem report on a phenylketonuric patient.

Urine from 8 of the phenylketonuric patients was examined by means of chromatography and was found to contain a high level of taurine, sarcosine and "Substance A." An increase in the urinary output of these three substances has been observed on occasions during or shortly after gastro-enteritis with liver involvement. The identity of "Substance A" is unknown, but it is known to be a nitrogen-containing compound.

Delay, Pichot *et al.* (1947) draw attention to the extrapyramidal signs and choreoathetotic movements seen in Kinnier-Wilson's disease, in the pseudosclerosis of Westphal-Strümpell and in phenylpyruvic oligophrenia. Delay and his co-workers point out that it is interesting to compare the hepatic lesions in the former two diseases with the pathological findings of Myle, Coquet *et al.* (1944). Delay *et al.* (1947) carried out a galactose tolerance test upon one patient suffering from phenylpyruvic oligophrenia. The result of the test was similar to that found in acute hepatitis.

The present writer carried out galactose tolerance tests for liver function on 12 patients of her series (Cowie, 1950).

Intravenous galactose tests were also performed on 8 of the phenylketonuric patients. The method used was on the same lines as that of King and Aitken (1940).

Galactose was administered, either orally or intravenously, to a fasting patient, in amounts varying according to the bodyweight. The blood-level of galactose in the subsequent two hours was assessed at half-hourly intervals.

The results obtained are given in Table V. The galactose was administered orally in 6 cases. This method was preferred, since the galactose after absorption from the gut passes directly into the portal vein.

TABLE V.

Patient.	Galactose. gm.	Route.	Blood galactose, mg. per cent. 0 hrs.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Liver dysfunction.
B. C—	50	Oral	0	7	7	33	8	−
F. W—	25	,,	0	90	48	40	..	+
I. S—	25	,,	0	0	0	0	0	−
	50	I.V.	0	57	0	..	0	−
M. W—	25	Oral	0	6	20	20	..	±
D. T—	50	I.V.	0	77	33	5	2	−
A. J—	35	Oral	0	30	72	63	6	+
C. B—	25	,,	0	12	36	81	72	++
P. Ph—	50	I.V.	0	15	0	..	0	−

In 3 cases strongly positive results were obtained, indicative of liver dysfunction Each of these cases gave results within normal limits when tested previously by the galactosuria method. A fourth case gave weakly positive results, possibly indicative of slight liver dysfunction.

The finding of abnormality of structure in the living liver would add much weight to the hypothesis wherein the liver is cited as being the possible seat of metabolic disturbance in phenylpyruvic oligophrenia.

Liver biopsy was carried out on two of the patients of the present series. The writer selected the patient Francis W— for biopsy because his liver edge was palpable half an inch below the right costal margin, and there was corresponding liver dullness. The liver biopsy was made through a 2-in. incision and a small wedge was removed. The report of the examination of the material by Dr. Martin Bodian is as follows :

"*Naked eye examination.*—The specimen comprised a small wedge of hepatic tissue taken from one margin of the organ. It was a light cream colour and showed some areas of congestion.

"*Microscopy.*—Chronic inflammatory cell infiltration of the larger portal tracts and slight thickening of the connective tissues of the central vein are present, and these serve to accentuate slightly the lobular architecture of the organ. The reticulin pattern is within normal limits, but the network of strands is rather thicker and more prominent than usual, and shows moderate condensation on the surface of the portal tracts. The hepatic cells are of normal form in some fields, while in others they display a shrunken appearance. The latter zones are most obvious around some portal tracts, but are also present elsewhere. A sprinkling of binucleated liver cells can be found. Glycogen storage appears to be adequate, and there is a fine diffuse fatty change, most marked in the peripheral parts of the lobules. Sudanophilic material also occurs in the intimal region of an artery and in the wall of another structure—probably a vein. There is no retention of bile."

The second biopsy was carried out on the phenylketonuric patient, Carol B—. The report by Dr. Martin Bodian runs as follows :

" Microscopical examination of the liver biopsy revealed no striking abnormality. The cells were normal, the reticulin framework was normal, the glycogen content was normal. There was a slight excess of fine and medium-sized fat globules dispersed fairly equally throughout the lobules."

Neither biopsy revealed any gross abnormality. This is in keeping with the negative findings of the induced galactosuria liver function tests. The fine diffuse fatty change in the periphery of the lobules in Francis W—'s case, and the slight excess of fine and medium fat globules in the lobules of Carol B— are interesting findings in view of the post-mortem findings in the liver by Myle, Coquet *et al.* (1944).

The Basal Metabolic Rate in Phenylpyruvic Oligophrenia.

Reports of the depression of the basal metabolic rate in phenylketonuria were published in France on two occasions (Delay *et al.*, 1947; 1948). In both instances the basal metabolic rate was depressed to — 27 per cent. The writers state that the true level may have been even lower than this, since the restlessness of such patients tends to give a higher result than would a recording of their truly basal metabolic rate.

Himwich and Fazekas (1940) found depression of cerebral metabolism in 15 cases of phenylpyruvic oligophrenia, using a method in which the oxygen content was measured in blood flowing to and from the brain. Such a lowering of cerebral metabolism may have been due to a general lowering of metabolism in the body.

Estimations of the basal metabolic rate were attempted in the cases of all of the 15 patients of the present series. In 12 cases no reliable results were obtained owing to the complete lack of co-operation of the idiot patients.

Derek T—, of imbecile grade, co-operated fairly well. On occasions where he was most co-operative, basal metabolic rates of + 23 per cent., + 24 per cent., + 26 per cent. and + 29 per cent. were obtained, but on all occasions he breathed more deeply than usually, and his pulmonary ventilation was high, being 7–10 litres per minute. His respiratory quotient was correspondingly high, varying from 1·06 to 1·17, this being accounted for by his increased effort of breathing, increased oxygen consumption and increased CO_2 removal. It cannot be stated that the results obtained in this case are significantly altered, since on no occasion did the patient relax completely, and the metabolism was therefore not truly basal.

Arthur P—, a phenylketonuric imbecile, was more co-operative than the idiot patients, but tended to be restless and frequently rejected the mouthpiece of the apparatus, causing leakage. Very few reliable figures were obtained, but his basal metabolic rate was probably slightly higher than normal, and his respiratory quotient was calculated as being 0·84.

John R—, of dull-and-backward mental grade, was very co-operative, when he had overcome some initial apprehension. The results obtained in his case are reliable. The pulmonary ventilation varied from 4·8 litres to 5·6 litres per minute on different occasions. The respiratory quotient was 0·81, 0·76 and 0·70 on different days. The basal metabolic rate was estimated as being + 13 per cent., + 12 per cent., + 15 per cent. and + 13 per cent. on different days. The depression of the respiratory quotient in this patient and in the case of Arthur P— may indicate preferential fat metabolism.

The hyperidrosis, hyperkinesis and exaggerated reflexes found in phenylpyruvic oligophrenia may suggest that hyperthyroidism is a possible component of the syndrome, although enlargement of the thyroid gland and other thyrotoxic signs are not features in any of the cases in the present series, nor are they reported in literature relating to the subject. An elevation of the basal metabolic rate fits in with this hypothesis.

On the other hand, since phenylalanine and tyrosine are raw materials required for the ultimate production of thyroxine, one might postulate a hypothyroidism in phenylpyruvic oligophrenia, although there is no clinical evidence

of this apart from the findings of Delay and his co-workers mentioned above. One of the patients of the present series was falsely diagnosed as a cretin at eight months of age and was treated with thyroxine for nine years, and his sister, also falsely diagnosed as a cretin, was treated with thyroxine from nine weeks to one year of age, and the condition of both of these patients has remained unaltered since the cessation of thyroid treatment. Studies of the blood cholesterol in patients of the present series provided no evidence of thyroid dysfunction.

All the figures obtained by the present writer indicate that the basal metabolic rate is increased in phenylpyruvic oligophrenia. This is in direct contradiction to the findings of Delay and his co-workers.

The Output of Phenylpyruvic Acid.

The urinary excretion of phenylpyruvic acid in phenylpyruvic oligophrenia is usually approximately 1 gm. daily (Penrose, 1946). The patient described by Coquet, Myle *et al.* (1944) excreted 2 gm. of the acid per litre of urine.

The present writer carried out quantitative estimations of the phenylpyruvic acid in the urine of the patients of the present series. The method used for the estimation of phenylpyruvic acid was that of Penrose and Quastel (1937). This method depends upon the formation of 2:4 dinitrophenylhydrazone in standard alkali solution, the resulting colour being compared with standard colours obtained with known amounts of phenylpyruvic acid. The results obtained are shown in Table VI.

Table VI.

Name.	Average daily output of phenylpyruvic acid (gm.).	Mental level.
John R—	0·5	Dull and backward
Derek T—	1·0	Imbecile
Lilian B—	1·0	Idiot
Arthur P—	1·1	Imbecile
Pauline P—	1·1	Idiot
Francis W—	1·3	,,
Georgina H—	1·4	,,
Carol B—	1·5	,,
Frances T—	1·8	,,
Pamela P—	1·8	,,
Margaret W—	1·9	,,
Joan S—	2·2	,,
Iris S—	2·3	,,
Brian C—	2·5	,,
Alan J—	2·9	,,

It is noteworthy that the phenylpyruvic acid output of the dull-and-backward patient should be so remarkably low. The number of patients in the series is too small for a conclusion to be drawn as to a correlation between the

amount of phenylpyruvic acid excreted and the mental level of the patient, but it is suggestive that the three patients of higher mental grade should be amongst those who excrete the least phenylpyruvic acid in the group.

In chromatography of the urine of the patients, although the urine of the dull-and-backward patient, John R—, was found to conform in other ways to the picture produced by the other phenylketonuric patients, the phenylalanine present, although excessive, was approximately only one-half of that excreted in the urine of the other phenylketonurics. This finding, together with the results of the quantitative estimations of the urinary excretion of phenylpyruvic acid in this patient, is in accordance with the view that the amount of phenylpyruvic acid excreted is an index of the amount of phenylalanine which is failing to be metabolized normally by the patient. It seems that John R— can metabolize phenylalanine at least twice as easily as any member of the series. His case indicates that phenylpyruvic oligophrenia does not follow an " all-or-none " rule ; the metabolic error may be present in patients in varying degrees.

Electroencephalography in Phenylpyruvic Oligophrenia.

Kreezer (1937) studied the electroencephalography of 8 phenylketonuric patients. He found a relatively high percentage of regular sequences made up of alpha waves of high amplitude and low frequency. The frequency averaged about nine waves per second, compared with an average of ten waves per second in the normal individual.

Kreezer stated that the low frequency found among phenylketonurics was of interest in the light of the fact that in phenylpyruvic oligophrenia there might be a diminished rate of oxidation due to lack of appropriate oxidizing enzymes. He quoted evidence that various factors, such as blood sugar, body temperature and basal metabolic rate, which might be presumed to correlate with rate of oxidation of brain cells, had a significant effect on the frequency of alpha waves, and that variation in these factors which might be expected to reduce the rate of oxidation in the brain cells led to reduction in alpha frequency. The reduced frequency of alpha waves in phenylpyruvic oligophrenia would therefore support the belief in reduced cerebral oxidation, probably due to a deficiency of essential enzymes.

Later, Kreezer (1939), after investigating the electroencephalography of various types of defectives and observing that abnormally slow occipital alpha rhythm was a common finding in low-grade cases, came to the conclusion that this dysrhythmia could be attributed to general immature cerebral organization.

Gibbs and Gibbs (1941) studied the electroencephalograms of 8 phenylketonuric patients. They found that even where there was no history of epilepsy, the records were similar to those commonly found in the case of epileptic patients during inter-seizure periods. They showed bursts of low frequency usually seen best in the parietal leads.

Jervis (1937*b*) writes that from examination of the electroencephalogram in phenylpyruvic oligophrenia, it appears that the extrapyramidal signs

commonly found may be referred simply to cortical atrophy, particularly of the frontal lobe.

Delay *et al.* (1947) report the electroencephalography of a phenylketonuric case, the interpretation of which was rendered difficult owing to the appearance of numerous rapid waves produced by the restlessness of the patient.

Delay *et al.* (1948) reported another electroencephalogram of a phenylketonuric child. This was a normal tracing. It was made when the patient was at rest.

Pichot *et al.* (1949) report a normal electroencephalogram, made on a female phenylketonuric imbecile, aged 17, at rest, the alpha-rhythm being twelve cycles per second.

Electroencephalograms were carried out on 13 of the phenylketonuric patients of the present series, and on 22 of their relatives, 2 of whom also suffered from phenylpyruvic oligophrenia.

Consideration was given to the possible relationship between epilepsy and phenylpyruvic oligophrenia.

Of the present series of cases 6 were epileptic. Of these 3 had epileptic electroencephalograms, 2 had normal or doubtful records, and 1 had no recording made. Of the electroencephalograms of the 9 patients without epilepsy, 7 were normal or doubtful, 1 was of epileptic type and in 1 case a satisfactory record was not obtainable. Of the 6 cases with epilepsy 1 had a parent with an epileptoid electroencephalogram with the presence of bursts of fast and slow activity. Of the 9 cases without epilepsy 1 also had a parent with an epileptoid electroencephalogram. From the data it seems that phenylpyruvic oligophrenia may be genetically independent of and unrelated to epilepsy, but epilepsy may be related to phenylpyruvic oligophrenia inasmuch that it appears as part of the clinical picture in a number of cases, as it often does in non-phenylketonuric mentally defective patients.

One of the purposes for carrying out electroencephalography on the relatives of the patients was to find whether abnormalities existed in the records obtained in the case of heterozygotes for phenylpyruvic oligophrenia. In the case of two parents, neither of whom showed any clinical signs of epilepsy, the electroencephalograms were epileptoid in character. Abnormalities were seen in only one other parent's record, where the abnormal findings were due to a previous history of brain abscess and operation.

A third point of interest in connection with the electroencephalography is the possible relationship between the abnormality of the record and the mental level of the patient. Such a relationship does not appear to exist. The dull-and-backward patient had a mildly abnormal electroencephalogram. Of the 2 imbeciles 1 had a normal record and 1 had an abnormal one. Of the 7 idiots without epilepsy all the records were doubtful or abnormal.

The records of the epileptics showed gross abnormalities which were probably related to the epilepsy rather than to phenylpyruvic oligophrenia. Leaving these records aside, the records of the non-epileptic patients tended to resemble each other in frequently being of low voltage and showing traces of rhythm on the alpha, beta and theta bands with little difference in the rhythmical patterns between the different parts of the brain, and poor rhythmical co-ordination between one area and another.

The electroencephalograms of the patients of the present series did not reveal any evidence as to a possible site of maximal disturbance in the brain in phenylpyruvic oligophrenia. Dr. D. A. Pond, who kindly carried out the electroencephalography, states that the abnormality in the electroencephalograms of these patients does not easily fit into any simple concept of the effect of the biochemical abnormality and that the records are not like those that one might expect in simple developmental retardation, nor in the case of a normal brain in a state of chronic chemical intoxication, although this is perhaps more likely than the former.

Tyrosine-feeding in Phenylpyruvic Oligophrenia.

Jervis (1937*b*) fed a phenylketonuric patient with 10 gm. of tyrosine, the diet being protein-free. He observed that the output of phenylpyruvic acid was not increased.

Penrose and Quastel (1937) fed tyrosine to two phenylketonuric patients. They found that administration of tyrosine did not consistently result in any increase in the excretion of phenylpyruvic acid. They found also that it was impossible to induce phenylketonuria in any control patients by feeding tyrosine. The findings seemed to indicate that in phenylpyruvic oligophrenia tyrosine is probably normally metabolized.

Three patients of the present series have been fed over a period of 16 weeks with 20 gm. of l-tyrosine daily to each patient. The tyrosine was administered in the diet of the patients. Quantitative estimations, for the assessment of phenylpyruvic acid in the urine, were carried out weekly during the experimental period. Three of the other phenylketonuric patients, corresponding as closely as possible to the tyrosine-feeders in age, sex and mental level, were chosen as controls, the patients being paired as follows :

	Receiving tyrosine.	Control patient.
(1)	John R—.	Arthur P—.
(2)	Lilian B—.	Joan S—.
(3)	Brian C—.	Alan J—.

During the experimental period the 6 patients concerned were kept under close observation for any change in their physical signs, behaviour or mental level.

At the end of the first week of the experiment, 24-hour specimens of urine were collected from the six patients. The method of Penrose and Quastel was used in each case to estimate the content of phenylpyruvic acid. In the case of the patients being fed with tyrosine, the readings obtained by this method were markedly increased, the value in one case being over four times as great as that obtained before the administration of tyrosine ; whereas the readings obtained from the urine of the control patients remained at their original levels.

Throughout the experimental period of 16 weeks, these values remained raised in the cases of the patients receiving tyrosine, and at the levels originally obtained in the control patients with little fluctuation. These results are given in Table VII.

TABLE VII.

Name.	Average 24-hr. output of phenylpyruvic acid prior to tyrosine feeding (gm.).	Weekly readings obtained during the period of tyrosine-feeding using the method of Penrose and Quastel for the estimation of phenylpyruvic acid (gm.).														
		1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	15th	16th
*John R—	0·5	0·8	0·8	1·0	1·4	1·2	1·0	1·0	1·0	1·6	1·3	1·0	1·1	1·0	0·9	1·0	1·0
Arthur P—	1·1	1·2	1·0	1·2	1·5	1·3	1·1	1·0	1·4	1·0	1·2	1·2	0·9	1·0	1·1	1·2	1·0
*Lilian B—	1·0	4·3	4·8	4·9	5·2	3·8	2·7	2·4	3·4	3·3	4·7	4·0	3·8	3·5	3·8	4·0	3·5
Joan S—	2·2	1·8	2·0	1·9	1·2	2·2	1·9	1·6	2·4	2·2	2·0	2·0	2·4	2·2	1·9	2·0	2·3
*Brian C—	2·5	3·3	3·5	4·0	4·2	3·7	3·0	3·2	3·8	3·6	4·4	3·6	3·6	3·2	3·4	3·4	3·8
Alan J—	2·9	2·8	2·5	2·9	2·4	2·4	2·6	2·5	2·7	2·9	3·0	2·8	2·5	2·8	2·9	2·7	2·4

* Tyrosine-fed patients.

The increased readings obtained in the cases of the patients being fed with tyrosine was due to the excretion of parahydroxyphenylpyruvic acid, this compound giving very similar chemical reactions, including the reaction with 2:4 dinitrophenylhydrazine, as does phenylpyruvic acid itself.

The mechanism of oxidation of tyrosine to parahydroxyphenylpyruvic acid occurs in the non-phenylketonuric individual. This was well illustrated by the feeding of 20 gm. of l-tyrosine daily to a non-phenylketonuric patient over a period of ten days. At the end of this time his urine gave an intense colour reaction with 5 per cent. ferric chloride solution. This was instantaneous on addition of the ferric chloride to the urine, and produced a very deep blue-green coloration which faded rapidly. The reaction differed slightly from the reaction between ferric chloride and phenylpyruvic acid ; in the case of phenylpyruvic acid the colour takes several seconds to develop, is less blue, and takes about half an hour to fade. The urine gave a reaction with 2:4 dinitrophenylhydrazine similar to that produced by phenylpyruvic acid. The urine gave a positive Millon reaction and a positive Briggs reaction. These two reactions are given by parahydroxyphenylpyruvic acid, but not with phenylpyruvic acid.

The present writer, who is non-phenylketonuric, took 20 gm. of l-tyrosine by mouth daily for three days. This did not lead to the urinary excretion of any substance giving reactions with $FeCl_3$ or 2:4 dinitrophenylhydrazine. It seems that a latent period of several days occurs before parahydroxyphenylpyruvic acid appears in the urine.

The finding that both phenylketonuric and non-phenylketonuric individuals metabolize tyrosine in the same way, by oxidation to parahydroxyphenylpyruvic acid, is in accordance with the conception that the block in metabolism occurs in phenylpyruvic oligophrenia at the stage of conversion of phenylalanine to tyrosine, and that the metabolism of tyrosine can proceed unimpaired.

During the period of the tyrosine feeding experiment it was observed that the two idiot patients receiving tyrosine, Lilian B— and Brian C—, became more active and hyperkinetic, and appeared to take more notice of their surroundings than formerly. This was not observed in the control patients, nor in the case of the dull-and-backward patient, John B—, who received tyrosine.

Eight weeks after the experiment was started, psychological testing was carried out on the patients concerned. In every case except one the mental level remained unchanged. In the case of one patient, however, Alan J—, who was not receiving tyrosine, there was reported to be " a slight increase on the previous assessment of his developmental level as estimated on the Vineland Social Maturity Scale."

At the end of the period of the experiment, 16 weeks after it was started, the following findings were made :

On examination of the three tyrosine-fed patients and their controls, no change in physical signs was observed. The head measurements were the same as those obtained prior to the experiment. The heights and weights of the 6 patients at the beginning and end of the experiment are given in Table VIII. The youngest patient of the 6, John R—, who received tyrosine, gained the most weight during the period of the experiment. Weight was lost by only one of the 6 patients, Lilian B—, who also received tyrosine. Two tyrosine-fed patients, Brian C— and John R—, and one control patient, Arthur P—, showed small increases in height. Growth, as assessed by measurements of height and weight, appeared to be independent of the feeding of tyrosine.

TABLE VIII.

Name.	Age at beginning of tyrosine feeding experiment.		Weight at beginning of tyrosine feeding experiment.		Weight at end of tyrosine feeding experiment.		Height at beginning of tyrosine feeding experiment.		Height at end of tyrosine feeding experiment.	
	yrs.	mths.	st.	lb.	st.	lb.	ft.	in.	ft.	in.
*Lilian B—	18	8	4	2	3	13¾	4	3½	4	3½
Joan S—	21	9	7	4	7	5½	4	8½	4	8½
*Brian C—	9	0	3	13	3	13½	4	1	4	1½
Alan J—	9	10	3	5	3	7¼	3	11	3	11
*John R—	7	9	3	12	4	1	4	1¼	4	2
Arthur P—	12	4	5	1½	5	2	4	7½	4	8

* Tyrosine-fed patients.

Electroencephalography was repeated on the patients at the end of the experiment. According to the records obtained it appeared that the feeding of tyrosine had not promoted cerebral maturation. There was evidence that some maturation had occurred in one of the control patients. The only new positive finding in the tyrosine-fed patients was seen in the case of the dull-and-backward patient, John R—, where epileptoid features, not previously found, were observed. It cannot, however, be assumed that these features were previously absent and were induced by the feeding of tyrosine. It is more likely that they were in a latent phase during the recording of the previous electroencephalogram, but it is not impossible that they were brought into evidence by an activating effect of the tyrosine.

At the end of the experimental period psychometry was repeated, using the same battery of tests as previously, except, to obviate the learning factor, in the case of the Stanford-Binet/Terman-Merrill Revision used for the two higher-grade patients, where Form L was substituted for Form M, which was previously used. The tests used included the Vineland Social Maturity Scale for the idiot patients ; Stanford-Binet, Porteus Mazes, Goodenough " drawing-of-a-man " test ; and Raven's Matrices for the higher-grade patients. In no case was there any significant change recorded since the previous assessment at the beginning and middle of the experiment.

Prior to the performance of this experiment tyrosine had only been fed to phenylketonuric patients over short periods and in small quantities (Jervis,

1937*b*; Penrose and Quastel, 1937). This experiment has served to show that no apparent therapeutic effect is produced in patients suffering from phenylpyruvic oligophrenia when tyrosine is fed in larger quantities and over a period of four months. It appears that after the human organism has developed for years in the "internal environment" of phenylpyruvic oligophrenia, no amelioration of the mental condition or physical signs can be brought about by the administration of tyrosine. Hope lies, however, in the case of the newborn phenylketonuric child. The youngest patient of the present series fed with tyrosine was already seven years and nine months old at the beginning of the experiment. Phenylpyruvic acid is not sought in the urine of infants as a routine measure; the discovery of phenylpyruvic oligophrenia is made, and then but occasionally, when the child has reached an age at which signs of mental defect show themselves. By this time the damage is done. The writer feels that every effort should be made towards an early diagnosis of the condition by a simple chemical test, so that possible therapeutic methods may have every chance of fair trial.

Summary

Fifteen cases of phenylpyruvic oligophrenia were discovered at the Fountain Hospital, London. Examination of family histories led to the discovery of two more phenylketonuric patients in other institutions, not previously diagnosed as suffering from phenylpyruvic oligophrenia. On physical examination of the patients, observations of certain characteristics were made which had not before been described in the literature dealing with phenylpyruvic oligophrenia. The family histories were studied with reference to the mode of inheritance of the condition, and the search for a genetic linkage between the human serological types, previously limited to a study of the ABO and MN, groups, was extended to include investigation into the Lewis, Kell, Lutheran, S, P, Duffy and Rhesus groupings. The possible role of the thyroid in phenylpyruvic oligophrenia was discussed, and in this connection investigations into the basal metabolic rate and the blood chemistry of the patients were made. The blood chemistry findings also threw light on the problem as to whether the increased muscle tone of the patients was due to a low serum calcium level. The dilution of hair colour was measured by an objective method of evaluation. The possible role of the liver in phenylpyruvic oligophrenia was considered, both the structure and function of this organ being studied. Quantitative estimations of the output of phenylpyruvic acid were carried out, with a view to discovering whether there was any correlation between the amount of phenylpyruvic acid excreted and the severity of the mental defect. Electroencephalography of the patients and their relatives was carried out, with a purpose of finding whether abnormalities existed in the brain potentials of heterozygotes for phenylpyruvic oligophrenia; to find, if possible by this method, the site of maximal disturbance in the brains of the patients; and to establish whether any relationship existed between the mental level and abnormality of electroencephalogram. Electroencephalography was also used, together with psychological testing, quantitative analysis of the urine, and observations and measurements concerned with the physical state of the patients, to provide base-lines

for an experiment in tyrosine-feeding. The results obtained within the limits of this experiment were negative, but it is hoped that tyrosine-feeding will in the future be tried in the case of newly-born phenylketonuric infants.

Phenylpyruvic oligophrenia stands alone as being a condition in which a specific metabolic error is accompanied by mental defect. It is a clear-cut biological entity in itself, but at the same time is a complex study which is approached through the avenues of psychological and clinical medicine, biochemistry and genetics. The ultimate problem it presents is the nature of the relationship between the metabolic disturbance and the mental state.

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A COMPARATIVE STUDY OF THE DRAWINGS MADE BY VARIOUS CLINICAL GROUPS.

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I. Introduction.

In the nineteenth century considerable attention was devoted to the art products of psychotics. The approach to these interesting phenomena was, however, unsystematized and of little value to psychopathology. Prinzhorn (1922) described the collection of psychotic art at Heidelberg. His monograph on the subject is a classic, but it has been pointed out by Elkisch (1945) that his analysis was not carried far enough to produce significant diagnostic criteria. In five recent articles Anastasi and Foley (1940, 1941) have made a comprehensive survey of work done on the whole field of the artistic behaviour of abnormal people. They have pointed out the inadequacies of research in this sphere : the lack of control groups of normal people, the generalizations made from a few selected data, and the constant danger of reciprocal projection.

Rorschach workers have long been concerned with the analysis of imaginative responses, and quite apart from the question of the validity of their overall conclusions, they have developed useful categories of form, colour, content, etc., which at first sight it would seem fruitful to apply to the drawings of clinical groups. The Graphic Rorschach, as used by Grassi and Levine (1943), is well known, but it has a more specific purpose than the present study, which endeavours to apply some of the Rorschach categories to drawings produced outside the Rorschach situation, and freely adapts suitable categories from the work of Beck, Piotrowski, Klopfer and Hertz, as summarized by Elderkin Bell (1948). With these an attempt is made to analyse the artistic responses of subjects, in order to discover, *if possible*, significant variables which would differentiate between various psychiatric groups.

Analogous attempts at a diagnostic classification of drawings have been made by Lembke (1930), Pfister (1934), Traube (1937) and Schmidl-Waehner (1942), among others. Only in the last of these studies is any use of Rorschach categories made, and the groups studied are seldom strictly comparable to our own. The research of Ruesch and Finesinger (1941) on the relation of the Rorschach colour response to the use of colour in drawings would at first sight seem to be relevant to the present problem. However, the method which Ruesch and Finesinger employed in classifying the use of colour in drawings is so different from the present one that the results obtained are in no way comparable.

II. The Problem.

The aim of the present investigation is simply to see if Rorschach categories can be used to compare the drawings made by 60 boys and 42 adults in response to the Raven Controlled Projection Test (Raven, 1951). The boys were aged

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8 to 14 years, and had I.Qs. from 80 to 135. They were matched for age and intelligence in three groups of 20, which had been previously designated as "Normal," "Nervous" and "Uninhibited." According to Child Guidance Clinic reports, the nervous boys had "temperamental, educational or speech disabilities." The uninhibited boys showed near-delinquent behaviour. (The test records were those previously used by Barclay (1945).)

The adults were war-time patients at Mill Hill Emergency Hospital, and were thus not advanced cases. They were classified in official records as "anxiety states," "depressives," "hysterics" and "psychopaths." There were 9 male and 3 female anxiety states; 10 male and 2 female depressive; 5 male and 4 female hysterics; 4 male and 5 female psychopaths. These adult groups were not matched for age and intelligence.

III. Method.

The boys' drawings were randomized, and then assessed by both observers together. The child's own description of his drawing was consulted in each case, so as to obtain the maximum of information. A common definition for each category employed was arrived at by discussing each point of difficulty as it arose. The percentage of the page covered by colour, a detail, or the whole drawing, was calculated by using a transparent grid similar to that suggested by Fleischer and McV. Hunt (1941) for the location of Rorschach details. The grid was ruled off in one-inch squares, and covered the standard page used by each subject.

The method of assessment of all the drawings was the same, except that while the children's drawings had been classified by the two observers in collaboration, the adult drawings were assessed separately by each observer on the more subjective categories of form, movement, the relation of colour to form, depth or perspective, style, observers' appreciation, and serial effects. The agreement between the independent ratings was found by the formula:

$$\frac{\text{Mean No. of each subject's drawings with complete observer agreement}}{\text{Mean No. of drawings produced by each subject}} \times 100.$$

On this formula the agreement on the categories was: Form 98 per cent., movement 100 per cent., relation of colour to form 100 per cent., depth or perspective 98 per cent., style 95 per cent., observers' appreciation 48 per cent., serial effects 100 per cent. These figures were undoubtedly raised by the fact that the two observers had previously assessed the children's drawings together.* It seems doubtful if such a high level of agreement would have been obtained by observers assessing the drawings solely on the basis of the definitions given below. Although these provide a fairly close approximation to the standards of judgment used by the observers, they are objectively discriminating in all categories but that of "Observers' Appreciation."

IV. The Categories Considered.

The main aim was to adopt suitable variants and follow them through the various clinical groups for which drawings were available. For this purpose

* Effects of this kind have been described by Sherif (1935) and Schonbar (1945) in their experiments on the formation of group norms.

TABLE I.—*Assessment of the Drawings of the Clinical Groups.*

	N.	Nvs.	U.	A.	H.	D.	P.	M.	F.	B.*
I. *Distribution of the Subjects.*										
Number of male subjects in each group	20	20	20	9	5	10	4	28	0	60
Number of female subjects in each group	0	0	0	3	4	2	5	0	14	0
Total number of subjects in each group	20	20	20	12	9	12	9	28	14	60
II. *Output and Organization.*										
(*a*) Mean number of pages used	1·05	2·1	2·3	1·67	1·44	1·33	3·67	1·78	2·29	1·82
(*b*) ,, ,, of entities per page	1·05	1·65	1·83	3·23	1·67	3·67	5·22	3·50	3·36	1·51
(*c*) ,, percentage of each page covered by drawing	38	28	38	28	25	42	24	30	33	35
Percentage of drawings containing—										
(*d*) One large object only	43	11	38	13	17	8	14	13	12	31
(*e*) ,, small object only	10	12	3	25	22	16	7	23	8	8
(*f*) A large group of large objects	20	43	19	31	28	42	30	30	39	27
(*g*) ,, ,, of small objects	23	12	28	19	11	25	49	21	34	21
(*h*) A small group of large objects	5	6	1	0	6	8	0	5	0	4
(*i*) ,, ,, of small objects	0	17	11	13	17	0	0	7	7	9
III. *Form and Content.*										
Percentage of drawings—										
(*a*) With well-defined forms	75	40	26	71	50	67	61	62	66	47
(*b*) ,, content classified as—										
Botanical	35	25	31	29	44	18	13	26	25	30
Mountainous	23	16	24	4	22	8	15	6	21	21
Clouds, mist or rain	15	13	20	0	0	8	9	4	4	16
Water	30	29	42	8	22	11	17	11	20	34
Fire or smoke	5	19	41	13	11	3	14	11	7	22
Sun, moon or stars	8	15	22	0	0	0	6	0	4	15
Architecture	25	20	46	13	0	47	29	24	23	30
Domestic	5	1	25	10	0	49	8	25	5	10
Land vehicles	5	29	13	3	0	0	11	5	0	16
Water vehicles	28	42	47	4	22	11	6	10	10	39
Air vehicles	25	36	15	8	11	0	6	9	0	25
Weapons	18	43	27	17	11	0	17	16	0	29
Emblem	35	28	32	13	22	11	23	18	13	32
Title	10	2	7	8	0	0	0	3	0	6
Alphabetical	0	3	21	8	0	29	8	16	4	8
Number	0	0	7	0	6	17	6	9	4	2
Abstract	0	13	13	29	22	21	46	24	39	9
Scribbling	(not assessed)			8	11	8	21	8	19	(not assessed)
Anatomical	0	0	0	13	0	0	13	4	12	0
Human	30	48	43	44	33	29	57	37	46	40

(a) Depicted or described human movement	25	46	40	.	6	0	8	22	.	7	7	37
(b) ,, ,, animal movement	15	15	1	.	0	11	8	13	.	4	14	10
(c) ,, ,, inanimate movement (formless)	5	13	35	.	13	11	11	9	.	15	3	18
(d) ,, ,, ,, ,, (with form)	48	60	40	.	8	11	19	11	.	18	2	49
V. *Colour.*												
Percentage of drawings giving—												
(a) A pure colour response	0	0	1	.	0	0	0	0	.	0	0	0
(b) A colour response, form being subsidiary to colour	0	7	15	.	0	0	0	0	.	0	0	7
(c) ,, ,, colour being subsidiary to form	75	71	75	.	42	26	31	34	.	27	47	74
Percentage of subjects using—												
(d) Coloured pencils in addition to black lead pencil	70	90	90	.	42	33	33	56	.	32	57	83
Percentage of drawings in which—												
(e) A white area is used as a figure on a coloured ground	30	20	13	.	0	0	8	0	.	3	0	21
Mean percentage of the area of each drawing—												
(f) Left as enclosed white	58	45	41	.	47	63	57	57	.	55	57	48
(g) Coloured :												
Black	2	19	21	.	32	28	33	20	.	33	20	14
Red	5	5	4	.	4	3	2	2	.	4	1	5
Orange	0	1	0	.	1	1	1	1	.	1	1	0
Yellow	5	5	4	.	2	0	1	1	.	1	1	5
Green	7	10	12	.	6	2	2	15	.	3	11	10
Blue	15	6	7	.	5	6	3	4	.	3	8	9
Purple	0	3	6	.	1	0	0	1	.	1	1	3
Brown	8	3	4	.	3	0	1	1	.	2	1	5
VI. *Combination of Movement and Colour.*												
Percentage of drawings containing—												
(a) Both movement and colour	63	64	68	.	8	11	17	44	.	19	19	65
(b) Movement, without use of colour	5	21	5	.	8	11	8	11	.	12	3	10
(c) No movement, but use of colour	13	14	23	.	33	22	17	11	.	18	28	17
(d) Neither movement nor use of colour	20	1	5	.	50	56	58	33	.	50	50	9
VII. *Depth or Perspective.*												
Percentage of drawings—												
(a) With marked depth or perspective	23	16	18	.	10	33	40	21	.	22	33	19
(b) ,, slight depth or perspective	43	36	43	.	48	22	49	31	.	51	15	41
(c) ,, no depth or perspective	35	48	41	.	42	44	11	48	.	26	52	41
VIII. *Style.*												
Percentage of drawings—												
(a) In a primitive style	35	63	58	.	39	22	24	26	.	22	41	52
(b) ,, photographic style	60	37	41	.	53	44	64	47	.	59	41	46
(c) ,, sophisticated style	5	0	1	.	8	33	13	28	.	20	18	2

TABLE I.—*Assessment of the Drawings of the Clinical Groups (contd.).*

	N.	Nvs.	U.	A.	H.	D.	P.	M.	F.	B.*
IX. *Observers' Appreciation.*										
Percentage of drawings rated by the observers as—										
(*a*) Very pleasant	15	8	7	0	6	1	20	3	12	10
(*b*) Pleasant	50	42	31	50	61	37	15	42	40	41
(*c*) Indifferent	20	28	30	30	6	41	27	29	24	26
(*d*) Unpleasant	15	23	31	19	22	21	22	25	13	23
(*e*) Very unpleasant	0	0	1	2	6	0	16	2	12	0
X. *Serial Effects.*										
Percentage of subjects showing—										
(*a*) A marked recurrence of similar objects or themes	0	25	10	21	22	0	44	6	36	12
(*b*) A slight recurrence of similar objects or themes	5	5	20	4	0	0	33	12	0	10
(*c*) No recurrence of similar objects or themes	0	20	25	8	0	25	11	11	14	15

* N. = Normal; Nvs. = nervous; U. = uninhibited; A. = anxiety; H. = hysteric; D. = depressed; P. = psychopathic; M. = male; F. = female; B. = boys.

the categories used by leading Rorschach workers were selected and altered as seemed most appropriate. A number of additional content categories were included, and others eliminated. In the accompanying table it is possible to follow the main Rorschach categories of location, determinants and content. No attempt was made to arrive at a figure for the subject's mode of apperception, experience-balance, etc., as the material was so different from the usual Rorschach data.

The Rorschach method of classification was used in the present study simply as a guide to certain of the aspects of a drawing which could be conveniently described and compared. In most cases the definitions of the Rorschach categories have been radically altered to conform to the very different type of record assessed. This must be kept in mind in any attempt to relate the results to those obtained by Rorschach investigators.

Output and Organization.

The first task was to find the mean number of pages used by each subject ; next, to ascertain the mean number of entitites per page, an entity being any discrete object or systematically organized group of objects. The number of square inches of paper included within the outline of the drawing was then measured, to give the mean percentage of each page covered.

The size and grouping of the objects drawn were found by means of the grid. In these calculations the size of the object or group of objects was taken to be the smallest rectangle of inch squares on the grid which would frame the object or group. First, the size of the drawing as a whole was classified as *large* or *small*, according to whether it occupied more or less than one-third of the page. The drawing was then examined to see whether it was well integrated or could be readily analysed into a group of discrete objects. If analysable the component objects were in turn classified as large or small, according to whether most of them occupied more, or less, than one-twentieth of the page each. This gave, in all, six categories of organization, i.e. a single large object only, a single small object only, a large group of large objects, a large group of small objects, a small group of large objects and a small group of small objects.

Form and Content.

The drawings were next judged for well-defined forms. A drawing was described as having a well-defined form if the arrangement of its contour lines produced a total impression of clarity, definiteness and resemblance to the object or pattern which the subject said he had attempted to depict. This is undoubtedly rather a subjective definition, but no more adequate one seems possible at the moment. The problem of an objective distinction between " good " and " poor " form, in our classification, as in the Rorschach, remains to be solved.

The Rorschach content categories were taken over, some being discarded and others added as required. All drawings containing trees, grass, fruit, flowers, etc., were classified under botanical content. Hills, slopes, cliffs, etc., were put in the mountain category. Water included all forms except rain.

All man-made edifices came under architecture. Interior decorations, household effects, etc., were classified as domestic. Vehicles were differentiated into land, water and air types. Weapons included all military vehicles. Flags, insignia, etc., came under emblem. The title was defined as words set apart from the drawing describing it. All letters and words in the drawing not coming under this classification were then designated as alphabetical content. All patterns, designs, mandalas, etc., were called abstract.

Movement.

Movement clearly depicted in the drawing or described by the subject was differentiated into human, animal and inanimate. The movement of inanimate objects was further classified according to whether the moving objects possessed little or no definite form (e.g., rain, smoke, etc.) or a definite form (e.g., motor-cars).

Colour.

Pure colour responses were noted, being defined as virtually formless coloured scribbling. Form-colour responses were divided into those cases where form was subsidiary to colour, and *vice versa*. The percentage of subjects using coloured pencils in addition to the black lead pencil was assessed. Where a portion of the white paper was used as a figure against a coloured ground, this was noted, and the mean percentage of the area of each drawing left as enclosed white, i.e. as a white figure bounded by a line or coloured area, was calculated. The relative quantities of the following colours used by each subject were also measured by means of the grid, and expressed as a percentage of the total coloured area—black, red, orange, yellow, green, blue, purple and brown.

Combination of Movement and Colour.

This was covered by the use of four categories, comprising the use of both movement and colour, movement without colour, no movement but use of colour, and finally neither movement nor use of colour.

Depth or Perspective.

A three-fold classification of *marked*, *slight* and *no* depth or perspective seemed possible. To have marked perspective, a drawing had to convey an impression of tri-dimensionality. The central object had to possess marked figural qualities, appear tri-dimensional in itself, and stand out against a differentiated ground. If the figure-ground relationships were less evident or distorted, or if only the figure appeared tri-dimensional, no background being shown, the drawing was rated as having slight depth. If, on the other hand, the drawing was flat, with no attempt or a complete failure to portray a third dimension, it was said to possess *no* perspective.

Style.

Naïve representation of human beings and houses, distortion of perspective, etc., were held to be indications of a *primitive* style. Fairly accurate conven-

tional representation was designated as *photographic*. A *sophisticated* style was shown in economical and expressive use of line.

Observers' Appreciation.

The observers rated the drawings according to their personal affective reactions as very pleasant, pleasant, indifferent, unpleasant, or very unpleasant. This is, of course, a highly subjective category, and is therefore of potential use in the assessment of the observers' personalities.

Serial Effects.

The drawings of each subject were scrutinized for perseverative effects, and a three-fold classification made of those subjects who showed a marked, slight or no reccurrence of similar objects or themes.

V. Tabulation of Results.

In the accompanying table the drawings made by the following groups of subjects are compared with respect to the categories defined :

20 Normal boys . .	(N)	12 Anxiety states . .	(A)
20 Nervous boys . .	(Nvs)	9 Hysterics . . .	(H)
20 Uninhibited boys .	(U)	12 Depressive states . .	(D)
		9 Psychopaths . .	(P)
All 28 male patients .	(M)		
All 14 female patients .	(F)		
All 60 boys . . .	(B)		

In arriving at the figures given in the table, the unit of calculation was always the complete artistic response of each subject, not the single page of drawings. For example, in calculating the percentage of drawings with clearly defined forms in the group of uninhibited boys, a separate figure was calculated for each subject of the percentage of his drawings which contained well-defined forms. The twenty separate percentages were then averaged, and the resulting mean figure for the group as a whole was entered in the table. In this way, the more fluent subjects did not affect the result unduly.

The heterogeneity of the groups rendered them unsuitable for further statistical treatment. Differences in the incidence with which certain categories were noted in the drawings made by various groups studied are, however, interesting, and may in some cases be of potential diagnostic value.

VI. Inter-Group Comparisons.

Limitations of the Data.

The results are throughout subject to the following limitations of the available material.

(1) The number of subjects within each group was not large, and in the adult groups the relative frequencies of males and females varied considerably, two-thirds of the males being anxiety and depressive patients, and two-thirds of the females being hysteric and psychopathic. This has led, in a number of cases, to a strong probability that certain apparent sex differences in the drawings might be an outcome of the clinical groups into which the subjects

fell, and conversely, that clinical differences have been distorted by the varied proportion of males to females in each group.

(2) There is a distinct need for a control group of normal adults to be tested for comparison with the clinical groups studied. The age and sex comparisons are made mainly for the sake of completeness.

(3) An average of two pages of drawings was obtained from each subject, with a range of from one to nine pages. In view of the great changes which sometimes took place in the drawings of the more fluent subjects, this average seems hardly sufficient.* Judging by experience, it appears that for further studies of this type, each subject should produce a minimum of four pages of drawings.

(4) Certain seemingly inevitable difficulties were found while using the transparent grid to assess the areas covered by various objects drawn and colours used, especially the latter. In cases where an area had been scribbled over, or one colour of shading overlapped on another, the assessment of the area covered by black, enclosed white, green etc., was necessarily subject to error.

Differences in the Three Groups of Boys' Drawings.

It has been comparatively straightforward to distinguish the ordinary from the deviant groups by their drawings, but less easy to differentiate the two deviant groups from one another. The normal boys were less fluent in their artistic production than the others, but more careful. They drew one large object or group of objects with well-defined forms depicted in a conventional photographic way. Their drawings were mainly either black and white outlines, or contained carefully coloured (not black) shading. The drawings of the *nervous* boys occupied less of the available space on the page than those of the others. They often drew large groups of large objects, seldom single large objects. They also often drew weapons, while their drawings sometimes contained movement without colour, and were liable to show marked recurrence of themes. The *uninhibited* boys often drew houses, both from the outside and the inside, fire, smoke, numbers and letters of the alphabet. Their drawings tended to contain poorly-defined forms, which were sometimes subsidiary to the use of colour.

Differences in the Four Groups of Adult Patients.

Of the four groups, the clearest pictures obtained were of the depressed and psychopathic patients. It was rather difficult to distinguish the drawings of the anxiety and hysteric patients from one another and from the other groups. The *anxiety* patient's drawing especially had only one distinguishing characteristic not also found in that of the hysteric, namely, that it was rather more likely to contain movement without colour. The *hysteric* patient drew fewer objects or groups of objects on his page than the others, and tended to show botanical but not architectural objects. The *depressed* patient tended to cover more of his page with his drawing than the others, some of his drawings being of the "horror vacui" type described by Prinzhorn (1922). He tended to

* Schmidl-Waehner (1942) points out that "We cannot emphasize too strongly that the interpretation of only one drawing of a child is insufficient and may be completely inaccurate."

draw architectural and domestic objects, letters of the alphabet and numbers, and nearly all of his drawings possessed some degree of perspective or depth. The *psychopathic* patient used more pages than the others, and drew more objects or groups of objects on each page. He tended to draw large groups of small objects, abstract shapes and human beings, more of whom were shown as moving than in the other groups. His drawings often contained both movement and colour.

Sex Differences in the Adult Patients.

The *male* group tended to produce rather a greater proportion of drawings containing one single small object. Their content more often depicted domestic scenes, land and air vehicles, weapons and letters of the alphabet. Their drawings more often contained inanimate movement, and made greater use of black and red. In general, the drawings tended to show slight depth or perspective, photographic style, slight recurrence of similar objects or themes, and to be graded by the observers as indifferent or only slightly pleasant or unpleasant.

In the " continuous classifications " of perspective, style, serial effects and observer's appreciation, the drawings of the *female* group tended to include more extreme examples. They also showed a preference for drawing large groups of large or small objects, and the content was more often of the mountainous, water, abstract, scribbling and anatomical types. They drew more animal movement, more often using the coloured pencils, especially green and blue, and showing colour without movement.

Differences Between the Boys' and the Men's Drawings.

The *boys'* drawings contained a smaller number of entities on each page than those of the men. The boys more often depicted a single large object, and mountains, clouds, mist or rain, water, fire or smoke, sun, moon or stars, land, water or air vehicles, weapons and emblems. Their drawings more often showed movement of all kinds, and they made much greater use of the coloured pencils, especially green and blue. This use of colour occasionally predominated over form. They fairly often used a portion of the white paper as a figure against a coloured ground, which the men hardly ever did. Most of the boys' drawings were of a primitive type, and tended to show rather less depth or perspective and more thematic recurrence than those of the men. More of the *men's* drawings depicted a single small object, and possessed well-defined form. The content of their drawings was more often domestic objects, letters of the alphabet, numbers, abstract shapes, scribbling and anatomical objects. The men used more black than the boys. The men's drawings contained a greater degree of depth of perspective ; most were of a photographic type, while drawings of a sophisticated type were also fairly common.

VII. Comparisons with Results of Other Investigations.

Certain comparisons with the results obtained by Rorschach investigators may be of interest. The use of a part of the white paper as a figure against a coloured ground (e.g. where the outline of a cloud has been pencilled in and the

enclosed space left blank, the surrounding paper being coloured blue to represent the sky) corresponds to the Rorschach "S" category. This "intermediate form" or "space detail" is described by Rorschach (1942, p. 39) as "most common in stubborn, eccentric normals and in negativistic schizophrenics . . . S answers always indicate some sort of *tendency to opposition*." The groups of adults considered included no schizophrenics, and it is interesting to note that this type of response is hardly ever recorded of them. Conversely it seems rather odd that this type of response should appear so often among the groups of boys, especially the normal ones. It may be that by adapting the Rorschach classification to describe different situations we have produced a category whose diagnostic significance, if any, may not be related to that of the original. The point at least seems worthy of further study.

Maclay, Guttman and Mayer-Gross (1938), in their article on "doodling," describe a type of drawing which they found and designated as "*the mescaline type*." This resembles the images reported by patients under the influence of mescaline, and consists of a series of identical shapes drawn side by side and often gradually increasing or decreasing in size. This type of drawing was encountered in four of the subjects, namely, one from the uninhibited group of boys, one female anxiety patient and two female psychopathic patients.

The "horror vacui" type of drawing described by Prinzhorn (1922), in which all the available space on the page is carefully "shaded in" was produced by three of the subjects, all three being male depressed patients.

VIII. Comments and Conclusions.

Pursuing the idea that in comparing drawings we really compare what people see in them and say about them (Raven, J. C., 1951), the writers have used the Rorschach categories as a basis for assessing similarities and differences seen in people's drawings. The numerical data accompanying the present communication are intended to illustrate how far categories of this kind can be applied to the comparative study of drawings rather than as evidence that any particular characteristic can be regarded as indicative of a particular type of personality or clinical group. Deductions from the results obtained are intended chiefly to indicate the differential usefulness of the various categories considered. It may be felt that certain aspects of the drawings have been inadequately dealt with, while others have been over-emphasized. For example, Schmidl-Waehner's (1942) treatment of movement in children's drawings is more exhaustive than the present one, while Ruesch and Finesinger's (1941) assessment of colour responses is simpler. It seemed desirable at the outset to consider as many categories as possible, rather than to omit or elaborate any which might prove to be of differential value, at the expense of making the tabular data appear cumbersome.

In the categories of output and organization certain zero percentages (i.e., the absence of certain types of drawing in certain groups) may be of interest; for example, no normal boy drew a small group of small objects. These categories appear to be unaffected by age and sex.

Inferences concerning the twenty-one content categories are limited by the restricted frequency of their appearance. Few subjects titled their drawings or introduced anatomical details, and little can be deduced from the slight differences noted. Some content categories, however, show noteworthy differences. Fire and smoke was depicted by the uninhibited boys far more often than by the boys in any other group. Architectural and domestic details were drawn by depressed adults more frequently than by other adults. Weapons were drawn most frequently by nervous boys, not at all by women or depressed adults. Abstract designs were drawn chiefly by the psychopaths, but this was also characteristic of women, who formed over half of the psychopath group. Normal boys did not make abstract designs.

Many of the movement and colour categories appear differential. Formless inanimate movement differentiates the uninhibited boys from the other boys. Two categories of human movement and movement of inanimate forms are conspicuously absent from the drawings of men compared with boys. The use of colour seems to decline with age, while form subsidiary to colour only appears amongst the boys in the clinic group. The use of black shading differentiates the clinic boys from normal boys, who prefer blue.

Depth or perspective seems to be of considerable diagnostic value. Amongst adult patients its absence seems to characterize anxiety, while its presence seems to characterize depression.

Concerning style, primitive drawings seem characteristic of the abnormal boys, normal boys more often making photographic reproductions. There may also be sex and age differences. Sophisticated drawings occur chiefly amongst hysterical or psychopathic adults.

As regards serial effects, little can be said owing to the fact that few subjects produced more than one page of drawings.

While the foregoing categories have been made as objective as possible, the observers' appreciation is intentionally subjective, being almost entirely determined by the personalities of the observers themselves. It is, however, interesting to note that, amongst the boys, the normal group was preferred by the writers. The sex and age of the person producing the drawing had little effect upon the degree to which his or her drawing was appreciated.

The writers conclude that the results of the investigation support the argument that the Rorschach categories can be adapted to the comparative study of drawings, and open a line of inquiry meriting further investigation.

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PSYCHOSES IN CHILDHOOD.

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In the early literature of mental defect there are allusions to behaviour, shown by defective children, which would now tend to be regarded as psychotic. This is probably one factor which has led psychiatrists into thinking of psychosis in childhood as an exceedingly rare occurrence. It now seems at least possible, if not probable, that many cases of early psychosis have been missed because the end-result has been equated with mental defect. In a sense it could be so classed since psychotic children are very often rendered ineducable by reason of their disorder, which sometimes seems to date "from birth" (Kanner, 1943), and in others certainly arises at an early age. However, the term "arrested development of mind" is less applicable, since the mind of the psychotic child appears to develop in a distorted and unbalanced way, showing some faculties to be absent and others apparently developed in a precocious manner (Bender, 1947).

I know of no completely satisfactory definition of childhood psychosis. It is far from satisfactory to borrow the terms used for adult disorders, only to say that many of them do not apply. Since the impact of the disorder is on an immature and therefore not yet integrated personality, the result is both an arrest in immaturity, and an extensive disruption of the formative patterns of personality. Certain capacities, notably that of object-relationship, are most severely affected. Sometimes muscular co-ordination seems to be exceptionally well developed, perhaps because it functions without the brake normally supplied by the need to conform to an environment. Speech is usually severely affected, rote memory often surprisingly well sustained.

Perhaps psychosis in childhood can best be defined as a disorder, sometimes apparent from birth or from a very early age, and sometimes occurring as a deviation interrupting an apparently normal development, which affects the total organization of the child and his further development, so that he becomes unable to relate himself normally to either people or things.

These cases are still described in the literature as very rare. Both Bender and also Kanner, working in the U.S.A., stress that this condition is commoner than was supposed, and that has been my own experience, especially since drawing my cases largely from paediatric sources. These children appear to their parents ill, disordered, and different from any normally developing child, and so they tend to be taken to hospital.

The merely backward child seems to be a slower and clumsier edition of his better-endowed siblings. The psychotic child has a peculiar quality which is recognized almost from the onset of his disorder, but which is harder to pin-point in the infantile cases since so little is demanded of the infant and very young child. Of Kanner's reported cases (Kanner, 1944) which he regarded as

congenital, nearly all were referred for an obvious developmental failure, such as not acquiring speech at the normal age, or because backwardness was feared for some reason.

Where this happens, and the peculiar features so distinctive of psychosis are not recognized, the label of backwardness tends to stick. It is suggested that if a really accurate picture of the early development could be reconstructed for all the patients in any one hospital for defectives, a large number whose condition in childhood was primarily one of psychosis would be picked out. Earl, in 1934, pointed out that idiots were prone to psychotic episodes, but although they may reach the same end-point, the primarily psychotic child is not seen as abnormal until the onset of his illness.

It is therefore possible to hypothecate a series in which a child may be affected by the psychotic process so soon after conception that his illness is already in process at the time of his birth. His whole pattern of development will be subject to the distortions imposed by this illness. He will clinically be represented in the series as a case of Kanner's early infantile autism. Somewhere in this series will come those children whose early development is recognized as fully normal until they reach, say, the age when they are expected to begin to talk. Speech may even have begun hopefully, but the child does not progress towards using his speech to express his wants and his feelings. His words are often a list of names or phrases which he repeats. Even this may die away and he becomes mute. In such cases it is, of course, extremely important to exclude deafness, and the difficulties of being sure about this under school age are very cogent.

Beyond that again come children who, in response to some stress or perhaps without any apparent emotional problem, learn and develop normally for some years, and then have a psychotic illness in which they cease to speak, or in other ways demonstrate what Kanner has called "extreme autistic aloneness." These are children who suffer an intercurrent psychotic illness, a process which in a number of cases proves to be irreversible. Finally there are the children who are in some way predisposed to this disorder, and who become psychotic temporarily and who recover from it.

In each of these situations it would seem likely that we are dealing with some unknown factor, together with an inherited vulnerability, plus environmental difficulties leading to emotional distress. Melanie Klein (Klein, 1948) would, I think, regard the failure in object relationship, and in consequent capacity to form symbols, as primary, and she associates it with the failure of the small child's undefended ego to master the severest anxieties. In her view psychosis in early childhood is not so much a regression as a failure to progress beyond a phase of great danger. As a result of that failure, further development ceases. Since, however, this is a phase occuring as part of every child's development, it is still necessary to explain the situation within the child which allows fixation to occur at this early point.

Organic Psychoses.

Very much the same pattern of behaviour is shown, at first, in the organic syndromes, and in this group cases appear to start a degenerative process in

early childhood, with or without fits, which progresses towards a final dementia. This process may be rapid and relatively easy to diagnose, as in Schilder's disease, or may, where the whole process is long drawn out, provoke much clinical doubt. In the early stages of these illnesses the children often show the same features as in the psychoses without signs of organic involvement. First their speech is lost, then their outgoing interests and social capacity, with subsequent regression, and the failure to maintain social adaptations already learned. Motor capacity is preserved longer, but eventually runs to seed in a series of endlessly repeated stereotyped activities. The similarity in behaviour pattern is confusing in a cross-section of the illness, but can be seen clearly when a long view is taken and the deterioration carefully watched.

If it is true that in all these syndromes we are seeing the effect of a failure to maintain integration, then physical interference with function will obviously be one of the main gateways, but the path will lead downhill. In the purely psychotic reactions of early childhood it is of great interest that they are usually not progressive beyond a certain point. Either the condition is self-limited, or some equilibrium is reached, for the child remains healthy, and often very active in his limited and peculiar fashion. In the organic syndromes the condition progresses. In the literature, however, it will be noted that here and there, for instance in Tramer's description of a child whose mother kept a day-to-day diary (Tramer, 1934), and in Bovet and Jequier's cases (Bovet and Jequier, 1949), a unilateral extensor response was sometimes elicited, without other signs of pyramidal dysfunction. It is difficult not to confuse the issue by calling one disorder "organic" because it can be seen to progress, because the nature of the pathological process is known, if not the cause, and because post-mortem studies are available; and to call the other group psychoses without the prefix organic, merely because the disease is self-limited, because no organic process has been found to account alike for every case, and because post-mortem studies are usually not available.

To quote Schilder himself (1935), "Inferiority of the brain, acquired or constitutional, will lead to an increase in the emotional and intellectual peculiarities in a child's behaviour . . . primitive drives and emotions, as well as primitive motor tendencies, will therefore come out. . . . these pictures are reaction types of an undeveloped and pathologically inferior brain organization."

The terminology of the psychotic disorders is almost as confused as the pathology, but with less excuse. Where basic pathology remains unknown, classification tends to be based on clinical descriptions, attached to a name, and imperfectly adopted by subsequent users of this term, and the literature is full of such contradictions. For instance Heller (1908) described his original cases of dementia infantilis as being clear of epilepsy. He would class a deteriorating psychosis with fits in early childhood as a phrenasthenia aparetico-aphasica tardiva, but Kennedy and Hill describe a case of Heller's dementia with epilepsy. The differentiating criteria adopted in describing childhood psychosis do no more than emphasize how difficult it is to think clearly while so much of the disease process is unknown.

We shall, however, be quite safe in describing children who appear to be psychotic from birth, children who become psychotic in infancy, or in early

childhood, and children who develop psychosis in later childhood but before the age of puberty. As a general rule the age of 12 is taken as the upper limit of childhood, and any psychosis occurring for the first time later than this age is very possibly associated with the emotional and physiological disturbances so common around the time of puberty, and it seems better not to include them in the psychoses of childhood.

Is Childhood Psychosis always a Schizophrenic Reaction ?

If we take the definition of psychosis as a total derangement of the organism, then it is very likely that any disturbance as severe as this will, in the not yet integrated personality, precipitate splitting mechanisms, so that the disorganized picture becomes schizophrenic-like.

It is difficult to say why manic-depressive syndromes are so rare in early childhood. Again, turning to the analytic writers, Klein (1948), Scott (1948) and Winnicott (1945) all recognize depressive illnesses in early childhood, Melanie Klein going so far as to hypothecate the existence of the depressive position as a phase through which the child passes in the course of normal development. My clinical approach to children is not through child analysis, and therefore I am not equipped to support or refute her view, but I think we would all agree that very deep and disruptive reactions can be associated with states of mourning in young children. The clinical picture is perhaps most commonly seen in the pre-school child who is evacuated to a residential nursery, or as in the well known " Grief " film of Rene Spitz. The physical accompaniments of apathy and inertia, the inconsolable quality of the crying, the anorexia, the regression in personal habits, and perhaps most frightening of all, the rapid loss of any capacity to renew human contacts, is very strikingly like the depressed and depersonalized adult.

The manic flight is still more rare, and I can only recall seeing two really typically manic children. One of these was recovering from an acute encephalitic illness of unknown origin, and the other was an older boy of borderline intelligence, where the manic flight appeared to be a defence built around his very inadequate capacity.

The child analysts have led the way in propounding a psychopathology of the psychoses based on the analyses of normal and of disturbed children, and I do not doubt that we shall begin to look more intelligently on some of the hospitalization reactions as possibly related to depressive illness.

Nevertheless, at the present time to talk of a psychosis in childhood is, to all intents and purposes, a discussion around schizophrenic-like states in childhood.

The Condition Regarded as Congenital.

Kanner in 1943, and subsequently, has described a condition which he has named " early infantile autism," emphasizing that the children have never been otherwise than highly autistic, lacking in rapport, and in many instances mute. Most of these cases were referred for a supposed intellectual defect, or failure to acquire speech. The possibility of a deafness or an aphasia must be ruled out on clinical grounds. These children are not deaf, and they appear to

understand spoken language when their interest can be caught sufficiently to attend to it. There is no doubt that many of them will eventually find their way into schools for the mentally defective. In this group, since the child has never been quite normal, and is often very late in talking even where speech does develop, the diagnosis of mental defect is made and the unusual pattern of early development is lost. According to Kanner, the parents of these children are often highly intellectual ; indeed a high proportion of his recorded cases seem to be the children of psychiatrists !

One wonders, however, whether there are not as many of these children, from less socially favoured families, where the child has had to be institutionalized. Until this condition is recognized clinically, and looked for, the incidence will not be known. It is, however, these children that I would suggest are lost sight of in what is essentially a social diagnosis of undifferentiated mental defect. The interesting thing about them is their great similarity as a group. This will not be surprising if eventually they are traced to a unified pathological process, or to a disruptive process occurring at a particular point in development. Winnicott (1945), in an important paper which throws much light on the possible mechanisms of this condition, considers that around the age of five months the critical developmental level referred to by Klein is reached. One might therefore search the early histories for factors occurring around that date. Kanner notes the frequency of early feeding difficulties. In my own series of cases, 16 probably come into this category of congenital or near congenital cases. Analysing this admittedly very small group the following points seem to call for further inquiry :

Six children are in M.D. colonies, and 2 who are still under four look like graduating to one, i.e., half the group are loosely regarded as mentally defective. Of these 8 children, 3 had a history of threatened abortion with bleeding at dates between the third and sixth months of pregnancy, and 4 had a history of illness in infancy between four and a half and six months (post-natal), after which their development appeared to alter in a significant way. In only one of the eight " defective " children was there a perfectly clean sheet as regards the months of pregnancy and events in early infancy. Of this one child, the mother said that she appeared never to respond to her mother, who in turn admitted to having no feeling of affection for the child.

Of the remaining 8 who are distinctively psychotic and not likely to be taken for defective, 7 have unusual parents who are either highly intellectual and somewhat obsessional or admittedly psychopathic. In only 1 child out of 8 was the nurture and the parental background wholly normal and natural.

These few examples then, as far as they go, seem to support the thesis that in a high proportion of these cases the early history merits a careful analysis. In the group who emerge as *in effect* defective, the pregnancy history is not straightforward, or the very early development seems to have been interrupted by illness just at the date considered so critical by Winnicott.

Of course records could supply many hundreds of histories with similar disturbance where normal development seems to have been safely resumed. Maybe herein lies the unknown factor in these cases, either constituting a particular vulnerability to such disturbance, or an inherent inability to build

up defences against the disruptive process. These points are put forward as indications for further investigation ; it has been frustrating to try and apply the same sort of simple analysis to case-histories in the literature, only to find that half of them are for instance given without any reference to pre-natal or natal and immediately post-natal occurrences.

The cases which I have seen are consistently like those described by Kanner. In all there was the alert, intelligent expression described by him, with quick and well co-ordinated movement. All were autistic, and mothers often used the expression " living in a world of his own " or " he seems miles away." All showed a limitation of speech ; some with echolalia and a stilted verbalization, or a late developing speech which shortly died away altogether, and 5 have never spoken at all. All showed a tendency to stereotypy in movement and a restriction of interests, preferring above everything to watch moving objects ; 7 of them were " spinners " who either spun themselves round and round, or who developed an uncanny dexterity in spinning any round object again and again, content to watch it. While some of these children tended to cling to adults, none showed a normal affectionate response to tenderness. At the same time as unpredictable moods and fusses, all showed considerable indifference to their surroundings. Nine of them showed major sleep disorders during the years when the psychotic state was becoming established.

Psychoses Preceded by a Period of Normal Development.

In the children who developed a psychosis, the factor of vulnerability is peculiarly hard to assess, since their history prior to the illness has often not been noted with any particular accuracy. Once the child has become ill, however, the back history is reviewed, but always in the light of the illness which has subsequently developed. How much reliance can be placed on the history which begins " Now I look back I remember . . . ?" Again Kanner points out that, since a highly obsessional parent is one of the difficulties related to this condition, even those parents who do keep day-to-day records may be thereby demonstrating the harm they do by such meticulous scrutiny. Reverting to the Kleinian theory, if the development of schizophrenia in later childhood is related to a failure by the ego to sustain itself against severe anxiety, one source of anxiety is the intellectual parent who seems both remote and exacting to the child who so urgently needs to be sustained by a tolerant affection, capable of seeing him through his most negativistic and hostile phases.

A further difficulty arises over just this point of " vulnerability." We see fleeting moments of schizophrenic-like behaviour in many children, who fret and become disturbed over some major alteration in their lives. The normal child will often regress alarmingly during a period in hospital, at the birth of a younger sibling or at the loss of some loved figure, but the situation is surmounted, and could hardly be regarded as even a psychotic episode. From such little-noticed beginnings develops, in these especially vulnerable children, the full-blown schizophrenic attack. Naturally this raises the question, " Were they ever fully normal ?"—has the untoward occurrence merely highlighted a degree of rigidity and unadaptibility, present from birth, but until now not called to account ? The other doubt which other observers as well

as myself have felt is whether these children are recovered early schizophrenics who are first noticed in a relapse.

Sometimes, too, the disappointment of parents is all the greater because, before the psychotic illness, the child was a model child, an exceptionally good baby, something highly prized but with an almost unrealistic accommodation to parental hopes. Are we seeing here already the ominous passivity and the readiness to learn by rote, and to mimic, rather than to prosecute an ego-directed activity for its own ends? With such doubts in one's mind, going over the cases in the literature raises many questions of this kind.

However, there are undoubtedly children who eventually become psychotic after a clear history of months or years of normal development, without it having appeared at all likely that this would be so at an earlier stage. Again, very few have no precipitating cause to show, although the false reasoning of "post hoc, propter hoc" is difficult to guard against. Of 17 cases personally observed, only 3 began without any obvious cause. In 6 the psychosis developed out of an excessive reaction of protest and the arrival of another baby, and 2 followed the loss of a loved figure—in 1 the father who left home for an operation, in another a crippled elder brother who died. In 3 cases there was an ill-defined illness out of which the psychosis developed. In several others, changes such as an operation on the child with hospitalization, or the return of a father from active service, or a journey overseas, appear to have brought on the attack. In only 3 of the 17 cases was the psychotic illness itself the first sign of disturbance.

In all, speech is involved early and rapidly fades to mutism, and all but one child showed evidence of anxiety, unrest, fear of strangers, difficulty over feeding or elimination, but these distressing signs are more frequent, and the motor restlessness somewhat less marked, than in the earlier group. No less than 12 showed difficulty over sleep, often with periods of wakeful activity with laughter and talking to themselves during the night.

The youngest age of onset was one year, where the illness followed abruptly on an operation for intussusception. In the others the ages of onset ranged from one year ten months in a boy who became acutely hysterical, anorexic and anxious when his mother went into hospital to have a second baby, to four and a half, the latter being 1 of the 3 for whom no cause could be found. In the remainder the age of onset lies between two and three, thus falling into the notoriously difficult period of negativism in early childhood. The condition is only very slowly progressive, the eldest of the group being now fourteen. His condition as far as I can tell is quite stationary, except that, having no contacts, no speech, and no interests, he tends to become more difficult to manage as he gets older and stronger.

In none could I find any evidence of physical deterioration or brain pathology. Insulin was tried on one case, a dementia infantilis, and she unfortunately succumbed to a cerebral haemorrhage in an irreversible insulin coma, but the post-mortem showed no focal changes in the brain apart from those associated with her death. Three are in institutions for mental defectives, and the fourteen-year-old boy awaits admission to one. One boy appears to be responding favourably to psychotherapy.

The Psychotic Attack with ? Recovery.

Bender (1947), in her series of 100 children, states that a considerable number respond favourably to treatment or remit spontaneously. Her experience of cases is exceptionally large, but I can only say that in my own practice the results are anything but hopeful. This is partly due to the severity of the attack impact on the un-integrated organism, so that there is a likelihood of disintegration, or what Winnicott has called "falling to bits" of the personality. These long illnesses constitute such a formidable interruption to normal development that life can never be quite the same to the child who has experienced such an attack.

One boy had his acute attack at the age of four and a half. It was in the middle of the war, with air-raids at their height, but otherwise there was no clear precipitating cause. He remained a much disturbed child for some years, excessively dependent on his mother, anxious, solitary and almost speechless, grimacing, attitudinizing with regressed personal habits and disturbed sleep. He was seen again, and treatment began at the age of eight. He spoke in such a fragmented way that therapy was mainly effected by his drawings, which could sometimes be interpreted to him. He was at least able to make an active transference relationship, and through that to regain some measure of control over his disturbing fantasies. By nine and a half he was able to go to school, although he had no idea of reading or writing and required much special tuition. He made a very poor contact with other children, and often appeared weepy and afraid for no obvious reason. Now at thirteen and a half he is still in school and regarded as a timid and dull boy. He is quite without number sense, but he reads well and draws very well, though not nearly so well as when he was ill (Bender describes a similar heightened artistic ability during the acute illness). The most striking thing about him is his inertia and lack of initiative and his inability to make friends. During a holiday with normal rather aggressive children he became more active, but very paranoid about the wardens of the hostel. I think the likelihood of further schizophrenic attacks is very high indeed.

The other child is a boy now six, who went into a fever hospital at the age of five, and was unduly isolated because of severe poliomyelitis cases on either side of his cubicle. Although he is said to have been a normal child before this happened to him, he had in fact always shown a poor capacity for expressing feeling, and had been late (aet. 3) in learning to talk. His I.Q. on tests is approximately 80. After three weeks in hospital he was discharged, and during this time he had not been visited. His parents were quite unprepared for his condition on return, and it really seems as if this severe reaction had escaped notice in the hospital. He was mute in so far as conversation was concerned. He mumbled all day to himself, and played solitary and unintelligible games. On several occasions he appeared to be hallucinated, and perhaps for this reason he feared being alone, though he made little contact with anyone present. He showed great anxiety over going to the toilet, and his sleep was disturbed by periods of laughing, talking to himself and rocking. He appeared to be quite without response to personal contact, and his expression was dull and puzzled. This state of affairs lasted from February to August with very

gradual improvement, during which time he received psychotherapy. By September he became able to manage mornings at an ordinary school. He is still attending the clinic. It is open to question whether this is a schizophrenic-like reaction induced by solitary confinement, and a breaking off of all the personal anchorages on which he seemed unduly dependent. It is certainly a reactive psychosis, of which the pattern is not like that of a depressive state. In this child, too, therapy was directed to effecting a relationship within which the terrifying fantasies could be discussed, and so to speak disarmed, by being related to a reassuring adult figure. It was much more difficult in him to discover what was happening in his mental processes. When he went off into this "world of his own" it was impossible to follow his activities. They appeared to be detached and undirected, almost as if the higher integration at the cortical level fails or is rejected. This is not put forward as an anatomical explanation, so much as a description of what appears to happen. It may mean no more than the anaesthesia which marks the dissociation of, let us say, a hysterical limb.

When Russell Brain in his recent presidential address given to the Neurological Section of the Royal Society of Medicine (1950) said "the receptive function of the cerebral cortex is to provide us with a symbolical representation of the whole of the external world . . . and at the same time giving us similar symbolical information about our own bodies and the external world," and Melanie Klein can say of a schizophrenic child, "The ego has ceased to develop phantasy life and to establish a relationship with reality: after a feeble beginning, symbol-information in this child had come to a standstill," and Bender, "the disturbance is in identification processes; that is, difficulty in identifying oneself and thereby relating to the rest of the world is the essential psychological problem," it seems that we may all be very nearly saying the same thing.

The whole study of these children calls now for greater accuracy. They are no longer the rare phenomena they were thought to be. They are now known to be sufficiently frequent to require units for their care. Every possible approach needs to be made, physiological, biochemical, by means of E.E.G. and by means of therapeutic work, analytical and otherwise. Meticulous case-histories are required, and inter-family relationships come into the foreground, since these children demand such peculiar adaptations from the adults round them. The fact that a patient's behaviour appears unintelligible does not preclude us from recording our observations of it, and I cannot help thinking that most illnesses have seemed unintelligible to those who did not know all the facts. The bold application of speculative imagination, provided it remains linked to observed fact, is as likely to take us forward as any other method.

I would like to add a word of gratitude to the doctors, including the late Dr. Paddle, at Botleys Park Hospital, at Harperbury Hospital, Shenley, and at the Fountain Hospital, who so kindly allowed me to search for some of my material among the cases in their care, and who spent their time generously in helping me. For help with the medical aspects of many of these children's illnesses I am indebted to my colleagues at the Hospital for Sick Children, Great Ormond Street.

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AN ACCOUNT OF THE SZONDI TEST.

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More than two years have elapsed since the Szondi test material became available on the home market, but it seems that the widespread use of the test has been considerably delayed by the lack of a translation of Dr. Szondi's books (1, 2). Susan Deri's *Introduction to the Szondi Test* (3), which appeared last year, may, however, have enabled some who felt attracted by the test to acquaint themselves with it. The purpose of Deri's book is to give some guidance for the clinical handling of the test and for its interpretation. For the rationale she refers to Szondi's own books.

In this paper the attempt will be made to state briefly Szondi's theories, and to discuss with the help of a case from clinical practice the possibilities of the test and its place within a battery.

Dr. Szondi is a Hungarian psychiatrist. Before the war he worked in Budapest as a practising psychiatrist and analyst. He evolved his theories and his test 16 years ago and, together with co-workers and pupils, collected material of some 5,000 cases. When Hungary became a Nazi satellite country the team dispersed. Szondi now lives in Switzerland. He has written two books in Hungarian. They were translated into German and published in German. The first book was published in 1944, and is called *Schicksalsanalyse* (*Analysis of Destiny*), the second, published in 1947, has the title *Experimentelle Triebdiagnostik* (*Experimental Drive Diagnosis*).

Szondi states that his *Analysis of Destiny* is a bridge between genealogy and depth psychology. We owe depth psychology, says Szondi, to Freud, and he claims for himself only that he has found a new method. He sees the unconscious in three dimensions: the individual unconscious, that is the region explored by psychoanalysis, the family unconscious, that is the individual's inheritance, with which Szondi is concerned, and Jung's collective unconscious. Szondi calls his psychology a drive or need psychology. Like others before him he believes in drives and, therefore, in heredity. The novelty of his approach lies in the linking up of his drive scheme with genetic theories. In a recent review in the *Lancet* (4), Szondi's theories have been described as a "curiously animistic mixture of unorthodox genetics and unorthodox psychology." The writer feels by no means competent to criticize Szondi's structure, but it seems that of the basic assumptions much is either oversimplified and superseded or controversial and hypothetical (cf. Slater's article "Genetics in Psychiatry" (5)).

Szondi holds that not only bodily characteristics but the whole mental make-up are transmitted by the genes, and he builds his doctrine entirely on the recessive genes. He says that the recessive genes, although prevented by their dominant partners from manifesting themselves in their natural way, are none the less active. They have to find an outlet; they are unconscious

driving forces in us, and it is they who determine our choice in love, friendship, profession, sickness and death.

We choose a love partner or a friend because his recessive gene structure corresponds or is somehow related to our own. In the chosen profession the genes are satisfied in a sublimated form. For instance, a double dose of recessive genes may manifest itself in a pathological form and may turn a man into a murderer. With a simple dose of the same gene he will sublimate his drive; on a high level he may become a sculptor or surgeon, on a lower level a wrestler or butcher. Szondi has investigated the family history, friendships, professions, illnesses and nature of death of a great number of individuals, and in his book *Analysis of Destiny* (1) he presents the material of more than 90 cases, and attempts to prove his theory of the genetic predetermination of our choice. It can easily be seen that this theory raises problems of a philosophical, ethical and religious nature. Szondi counters objections by saying that only the framework of our destiny is inescapable, but that within that framework our ego is able to direct and modify our drives, and that the environment plays its part through the identifications which we form.

To try out these theories experimentally Szondi evolved the test. He uses psychological terminology. As is well known, the gene, although taken to be the smallest unit factor, has a male and a female component derived from the cells of the father and of the mother. Szondi calls the gene-partnership a drive-need or drive-factor. Two such factors pursuing the same drive goal form a drive or drive vector, e.g., needs of feminine affection and male aggression are combined in the sex drive. Szondi holds that the difference between being mentally healthy and ill is merely quantitative, and that all mental disorders are drive disorders which manifest themselves in people who have a double dose of the specific recessive genes, i.e., who inherit the same kind of recessive gene from both parents. It follows that in mental disorders the drives would manifest themselves in their purest form. To build up a system Szondi had to decide how many drives there were. He postulates that there are four main classes of independently inheritable mental disorders, and that each of the four classes can be divided into two sub-groups. Underlying these disorders are four drive vectors and eight drive factors. :

I.	Sexual disorders	(1) h omosexuality	Factor h
	Vector S	(2) s ado-masochism	,, s
II.	Paroxysmal disorders	(3) e pilepsy	,, e
	Vector P	(4) hy steria	,, hy
III.	Schizophrenic disorders	(5) k atatonia	,, k
	Vector Sch (ego vector)	(6) p aranoia	,, p
IV.	Contact or Circular disorders	(7) d epression-mania	,, d
	Vector C	(8) m ania-depression	,, m

Without wishing to attach too much weight to theoretical considerations, it may be noted in passing that Szondi's classification strikes one as being incomplete, and not in accordance with the grouping in current British psychiatry, to mention only the omission of the anxiety states, the classing

of epilepsy along with hysteria, and the grouping of sexual disorders in a class by themselves.

In accordance with his classification Szondi collected 48 photos of mental patients in six sets of eight photos. The number six seems to be arbitrary, but in every set of eight cards each of the eight drive factors is represented by one photo ; therefore, altogether each drive factor is represented six times. Each set of cards is numbered 1–8 on the back, and each card bears also the initial of the drive factor which it represents. The test consists in showing to the subject one set after the other, with the request to choose in each set the two photos he likes best and the two photos he dislikes most. The choices are recorded. Szondi reasoned that if his hypothesis that our choice in life is determined by our recessive genes was right, the reactions to the photos would depend on some similarity between the gene structure of the patient on the photo and that of the subject himself. The subject's structure would, therefore, reveal itself in his choice.

In his *Experimental Drive Diagnosis* (2) Szondi discusses the results of 5,000 cases which he and his co-workers have tested, and gives tables and syndromes. On the strength of these results Szondi considers that he has proved the genetic hypothesis he set out to test. This, however, may be a rash conclusion, and one feels that to accept it without reserve may be premature. It is conceivable that the hypothesis of the recessive genes may be partially or even completely false, and yet the test may be useful. *A priori* doubts on theoretical grounds should not stand in the way of a test which by a new approach may open up wider aspects of personality.

Turning now to the practical side. The administration of the test is easy and, in general, quick, but the test has to be repeated ten times to give reliable results and show dynamics, and although it can be repeated on consecutive days it takes up ten days at a minimum. This is a serious drawback, and restricts the full use of the test to institutionalized persons, or to out-patient who attend a clinic regularly over a long period. When the ten tests, called profiles, are completed, they are scored. The scoring presents no difficulties and is completely free from subjectivity—two distinct advantages over the Rorschach test, which should also make it more easily amenable to statistical treatment. (For a comparison of the advantages and disadvantages of the Rorschach test over the Szondi test see Susan Deri's paper " The Szondi Test " (6)). It will be remembered that there are eight drive factors, and that each of them is represented six times amongst the 48 photos. Four possibilities result from a subject's choice :

(1) +, positive reaction ; the subject likes two or more photos representing the same drive factor, and dislikes only one or none of the same factor.

(2) —, minus reaction ; the subject dislikes two or more photos representing the same drive factor, and likes only one or none of the same factor.

(3) 0, open reaction ; one or no choice of one factor in both directions.

(4) ±, ambivalent reaction ; two or more choices of the same factor in both directions.

As there are six photos of each factor the maximum choice, either + or —, is 6. The more one-sided the choice in a factor (e.g., 5s+ and no s—), the greater will be the tension in that factor owing to the assumed inherent polarity in the gene partnership represented by the factor. If, on the other hand, there is an open reaction (o, no choice), this is taken to mean that at the moment there is no tension because this particular drive factor has found open expression. The open reactions would, therefore, correspond to clinically observable symptoms or behaviour. In an ambivalent reaction (±) the patient experiences subjectively the simultaneous existence of opposing drives. For the causal factors, i.e., the factors responsible for symptoms, behaviour and uneasiness experienced by the patient, one has to turn to definite + or — choices.

It follows that the clinically observable data will be associated with the factors showing the greatest number of open and ambivalent reactions, and that their underlying causes will be associated with the factors showing the lowest number of open and ambivalent reactions. The scoring consists, therefore, in adding up throughout the ten profiles for each factor the open and ambivalent reactions, and then in arranging the eight factors in the arithmetical order of the sums found. The result is the so-called drive formula. For convenience this formula can be shortened down so as to show only the two extremes, i.e., the factor with the highest and the factor with the lowest $\Sigma o \pm$. This is expressed thus, e.g., $\begin{smallmatrix} s \\ k \end{smallmatrix}$, from which one should gather that for the patient's main symptom one has to turn to factor s, and for the deepest layer of the underlying causes to factor k. The next step is to inspect the four vectors one by one. The sums $o \pm$ reactions which are known from the previous operations are compared for the two factors of the vector, and the smaller figure is deducted from the larger one. The vectors are then arranged in the arithmetical order of the differences obtained. The vector in which the highest difference between the two factors occurred, together with the initial of the factor which showed the lower $\Sigma o \pm$ reactions and the sign which appeared most frequently in the factor represent what Szondi calls the drive class. Take for instance drive class Sch_{k-}. Sch would be the vector with the greatest difference in the $\Sigma o \pm$ between the two factors k and p, factor k would have the smaller $\Sigma o \pm$, and minus would be the most frequent reaction in factor k. The reasoning underlying the whole manipulation is based on the fundamental assumption that the two factors of a vector pursue the same drive goal. A great discrepancy in reactions between the two factors would tend to show that the needs which they represent are badly balanced in the individual. There is tension, and the least manifest or completely latent part of the need, that is, the one with only a few or no ± and o reactions, is supposed to be the dynamically more potent. Szondi attaches considerable importance to his concept of drive class, and in his *Experimental Drive Diagnosis* gives for the 16 main drive classes a detailed description of the characteristics of the individuals belonging to each class.

The scope of the paper does not allow for more than bare explanation, and it is hoped that the case which follows will make the working of the test clearer.

In spite of the apparent schematization it will be appreciated that the number of variations resulting from the four possibilities and the tenfold repetition is for practical purposes infinite, and that although each factor basically carries its own meaning, a satisfactory picture of an individual's personality can only be arrived at by considering the strength and the relationship of the choices in all eight factors and the changes occurring in the choices throughout the ten profiles. No claim is made to expert knowledge, and it is felt that greater familiarity with the test might have led to more comprehensive results. Some doubt was felt as to whether to present briefly the Szondi test results of several cases, or the results in full of one case only. Preference was eventually given to the latter method, because it made it possible to discuss the working of the test within a battery. The case presented was not chosen for its intrinsic clinical interest, but on the strength of its psychometric merits.

The Case of Marion.

Marion, 20 years, clerical worker and receptionist in a near-medical establishment. Mother died 2 years ago. Lives with father and older sister. Education : Polytechnic ; failed matriculation.

The patient was admitted to the Research Unit of the Clinic as a probable case of psychogenic rheumatism. She complained of pain in the back and leg. While the medical examinations were in progress she was submitted to a battery of tests. Only the data just mentioned were known to the tester.

Matrices.—Score 49, grade II, variability 4. Above average.

Wechsler-Bellevue.—Full scale I.Q. 114, verbal I.Q. 111, performance I.Q. 115.

The patient missed some questions, not from ignorance, but because she was upset by the test situation. The test made it clear that the patient's intellectual potentialities were above average, but that her emotional make-up made it difficult for her to cope with unusual situations.

Rorschach test.—27 responses, rejected card VII (frequently seen as two female figures or as female pelvis or womb). Anatomical perseveration ("lumbar region and spine"). M : sum C = 3 : $1\frac{1}{2}$. No true colour responses were given, only coloured photographs, but 41 per cent. responses for the last 3, coloured cards. 10 S (white space) answers ! Card III, strongly suggestive of two human figures, caused shock, and was handed back abruptly after the shortest time of exposure of all the cards. Some sinister content.

It was inferred that the patient showed a serious maladjustment in human relationship, that she was at odds with herself, and withdrew in order to avoid emotional entanglement, which she feared. Constantly prepared for flight. Morbid phantasy life. Hypochondriacal preoccupation. Artificial poise. No adequate outlet for affects. Strong depressive trends.

T.A.T.—Owing to shortage of time the test had to be carried out in the ward and was self-administered. The patient dealt with 15 pictures in five sittings. She had ten minutes for each story.

Only one story had a fairly happy ending. Complete family with happy family life : none. Four suicides (one attempted, three successful), one

murder. That the hero was the only child was mentioned seven times, the stern father as the cause of the drama three times (mother dead).

It appeared from the T.A.T. that for the patient the death of the mother had been a catastrophic event. It had shattered the childhood happiness, and the inner balance had not been restored. The father is seen as hard and completely lacking in understanding. Aggression is, however, not turned against him, but rather against the self. The patient is masochistic, wallows in her misery and daydreams of suicide. She is dreading the future. The picture which emerges is one of a lonely and immature person who is unhappy in her home environment and has not the courage to break away.

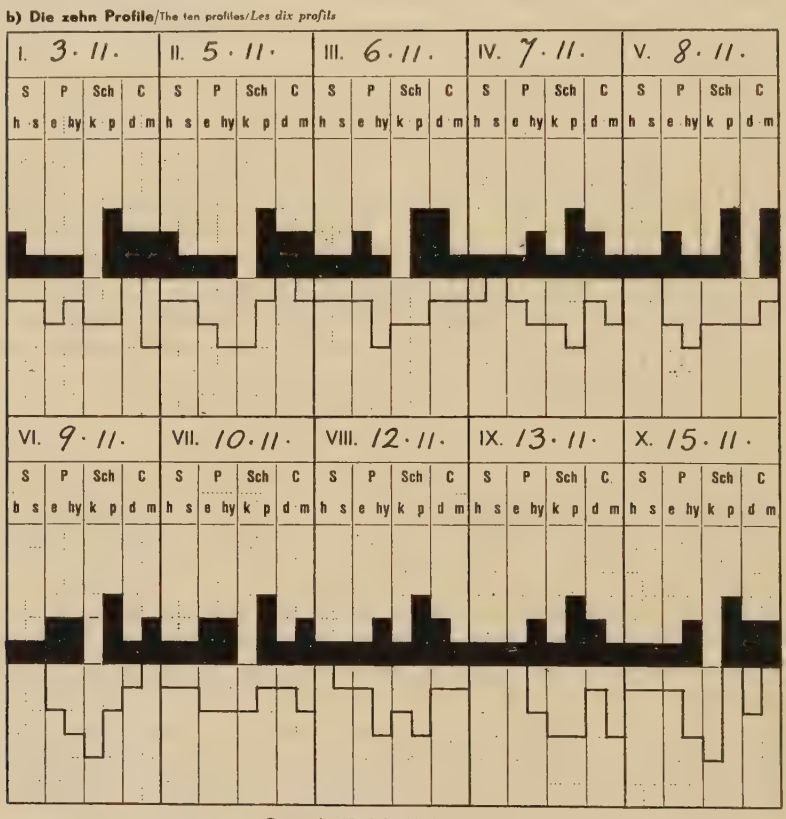
b) Die zehn Profile/The ten profiles/Les dix profils
I. 3 · 11 ·
II. 5 · 11 ·
III. 6 · 11 ·
IV. 7 · 11 ·
V. 8 · 11 ·
VI. 9 · 11 ·
VII. 10 · 11 ·
VIII. 12 · 11 ·
IX. 13 · 11 ·
X. 15 · 11 ·
S P Sch C
h s e hy k p d m

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FIG. 1.

Szondi test (Figs. 1, 2, 3).

If for the working out of the test the method which has just been described is followed, one arrives at a drive formula representing the patient's drive structure, and at a drive class. The drive formula once established can be looked up in Szondi's book, and the diagnosis represented by the formula can usually be found. In Marion's case the drive formula is $\frac{s}{k-}$ and the diagnosis

1949		S		P		Sch		C		Σ	Σ	Σ
Nov.	No.	h	s	e	hy	k	p	d	m	o	±	o±
3	I	+	o	−	o	−	±	+	±	2	2	4
5	II	+	o	−	−	−	+	+	+	1	...	1
6	III	o	o	+	−	−	±	+	o	3	1	4
7	IV	o	o	o	±	−	±	+	−	3	2	5
8	V	o	o	±	−	−	±	−	+	2	2	4
9	VI	o.	o	±	±	−!	±	o	+	3	3	6
10	VII	o	o	±	±	−	+	o	±	3	3	6
12	VIII	o	o	o	±	−	±	+	o	4	2	6
13	IX	o	o	o	±	−	±	+	−	3	2	5
15	X	o	o	o	±	−!	+	±	+	3	2	5
Σ	o	8	10	4	1	...	...	2	2	27	...	...
Σ	±	...	...	3	6	...	7	1	2	...	19	..
		8	10	7	7	...	7	3	4	...	...	46
		S_{ho}		Pe_{hy}		Sch_{k-}		Cd_{+}				
		2		0		7		1				

Drive class Sch_{k-}

o
Drive formula (full) : s

10

o+ o± − + ± − o ± +
h e hy p
8 7 7 7

+ ± o − + o ± −
m d k
4 3 0

Drive formula (shortened) : $\frac{s}{k-}$

FIG. 2.

"hypochondriasis, apathetic neurasthenia." The patient belongs to the drive class Sch_{k-} to which Szondi gives the name of "daydreamers and depersonalized individuals," and maintains that under a manic-depressive appearance they really are autistic and schizoid individuals. Not katatonics themselves, they are carriers of katatonia. He describes in detail the main characteristics exhibited by the persons belonging to this class, and their most frequent choices in the test. He mentions amongst their favourite professions "hotel managers, receptionists in sanatoria, druggists, beauty specialists." When the clinical aspects of Marion's case are discussed it will be seen that the diagnosis applies to her fairly well. The most frequent choices which Szondi mentions for drive class Sch_{k-} are correct in the patient's case, and she was a receptionist in a near-medical establishment. However, at least in the writer's limited

experience, things rarely work as smoothly. Moreover, the drive Linnaeus, as Szondi calls it in emulation of the great botanist's classification of plants, may not satisfy all workers. They may wish to arrive at a fuller understanding of that which is unique in the individual, and may perhaps find Szondi's book in that respect more confusing than helpful. Susan Deri's guidance to the interpretation is definitely more satisfactory, and in the following her principles were applied in the main. She lays the emphasis on the interpretation of the single choices and on their relationship one to another.

To begin the detailed analysis it has been found useful to know quickly for each vector how often each choice occurred within the series of ten profiles. This is shown on Fig. 3. Too great rigidity in a vector as well as too many

S			C	
8 times	o o	.	2 times	+o
			1 ,,	o+
2 ,,	+o	.	2 ,,	+−
			1 ,,	−+
			1 ,,	−±
			1 ,,	±−
			1 ,,	++
			1 ,,	o±

P			Sch	
4 times	o±	.	7 times	−±
2 ,,	±±	.	3 ,,	−+
1 ,,	±−			
1 ,,	+−			
1 ,,	−−			
1 ,,	−o			

Fig. 3.

changes can be taken as a pathognomonic sign. The vector with the greatest number of changes is C, the contact vector, which shows the individual's relationship to the environment, the d factor representing the possessive "anal" relationship, the m factor the clinging "oral" relationship (Deri, 3, p. 66). Out of 16 possible variations Marion chose 8, and three times she gave "mirror" reactions, these being complete reversals in the choice of the two factors, e.g., Fig. 2, profile IV d+m−, profile V d−m+. There is no stability, and an erratic, disturbed attitude in human relations can be inferred. The m+ reaction, which has been found to be the most frequent reaction of the healthy individual, appears only four times (Fig. 2, profiles II, V, VI, X), and the reaction o+, denoting an adult relationship with the environment, only once (profile VI). The m−, which in certain configurations may mean asocial behaviour, is represented once (profile IV), m± (profiles I, VII), the ambivalent reaction, shows complete uncertainty, and a state of affairs when pleasure can be derived neither from male nor from female friendships. This takes place at a conscious or semi-conscious level and the resulting unhappiness may lead

to suicidal ideas. Deri reports (3, p. 143) from therapeutic work with patients giving a m± reaction that they all had a "basically undecided sexual orientation," and this fits into the picture Szondi gives of the Sch_{k-} individuals as being unable ever to achieve a satisfactory identification either with the father or with the mother; they shift constantly from one to the other.

It is worth noting that in the T.A.T. Marion clearly changed in her identifications between mother and father, that she revealed strong suicidal phantasies, and that all her stories showed loneliness, unhappiness and bad human relationship. In the Rorschach test the disturbed social adjustment was an outstanding feature.

Inspection of the S vector (sexual vector) shows almost complete frigidity. Eight times an oo reaction was given. This means that there was no tension in the vector. The reason may be either that the need was satisfied through being acted out, or—and this is more likely as the reaction is almost constant—that Marion's tension in that vector is quite generally low. The patient has no mature sexual life, and is rather passive in her handling of the environment. She is not an active young woman, and lacks drive and push. Her needs are satisfied by what she has got. In conjunction with the knowledge gained in the Contact vector one may infer that in her sex life she is fixated on a childish level, will like to perpetuate the security of the parents' house and will not venture outside.

In the Rorschach test the lack of drive was evidenced by the reluctance and content of the movement (M) responses, "bad drawing of two people having a fight," in which the aggressiveness and the movement are almost completely nullified by the "bad drawing," "two people lying down," "two nuns sitting" (S, card IV). It is tempting to interpret the nun as a symbol of a sexless life led in the shelter of Mother Church. Animal movement responses (FM) were only given in the inquiry which followed the performance and not in the performance proper. Lack of drive was also shown in the T.A.T. more than once. In a suicide theme the patient wrote, "rushed to the window and *fell* out": note the "fell out" instead of "jumped out"; the active impetus stops short at the act itself. An unhappy young woman (picture 8 GF) dreams of a cheerless, desolate future instead of planning to bring about a change for the better.

The P vector (paroxysmal vector), which concerns emotional control, shows six different reactions and, therefore, lability. The e is supposed to show the way the violent emotions are handled, the hy deals with the finer emotions. If this is accepted it can easily be seen that an accumulation of emotions without outlet (— reactions) would lead to general emotional tension and diffuse anxiety which may take the vague form of hypochondriasis. From the three times hy— (profiles II, III, V) one may, therefore, infer that Marion has hypochondriacal thoughts, and the e—hy— reaction (profile II) shows her tension and anxiety. The tension is released by outbursts (7 times e o) which, are, however, unlikely to be of a very violent nature owing to the lack of driving energy shown in the so. They may rather have an exhibitionist tinge (the plus in the hy±). The ambivalent hy indicates that there is an almost conscious conflict whether to hide or disclose the feelings.

This agrees fully with the hypochondriacal preoccupation and the artificial poise which the Rorschach test revealed, and a completely illogical murder in the T.A.T. points in the same direction.

The most important and also most difficult vector is the Sch or Ego vector. The factors are k and p. Factor k represents the need to keep detached or, in Szondi's terms, the ego-systole, and the p the need to fuse with the environment, the ego diastole. From the choices in that vector the patient's ego pictures are derived. Szondi found that the choices varied with the patient's age, and he gives norms for different age groups. Both Marion's ego pictures (7 times k—p±, 3 times k—p+) are immature. The k—p+ shows her still as an adolescent who does not dare to live her own life although she would like to. The strength of the patient's conflicts can be seen from the loading of the Sch vector (Fig. 1), profiles I, III, V, VI; five choices of paranoid photos out of six. Profiles IV, VIII, IX, all six p photos were chosen. Profiles VI and X, four katatonic pictures out of six were rejected. This is the only factor where four choices appear in one direction, and that without a single counter-balancing choice in the other direction. The k is also supposed to stand for the rational ego, and the strong and constant k— means that the patient is inhibited, rigid, and forces herself to keep detached. The p± (7 times) according to Deri (p. 185), indicates suicidal tendencies, with paranoid features, the individuals giving that reaction "suffering feelings of unjust treatment," ". . . abandoned and not wanted enough." The ensuing unhappiness is the reason for the suicidal thoughts. Blame for one's own failure to establish satisfactory human relationships is put on others (projective quality of the p—). The suicidal tendencies were also present in the m±. The double threat, which in another configuration may be very real, loses much of its seriousness through the absence of drive (so) and the lack of accumulated violent affects (Fig. 1, e— never more than 2, and always counterbalanced by at least one e+). The k—p± is called by Szondi the "jealous envious ego picture." It is not surprising to find this ego picture in Marion. The patient is 20, attractive and of good intelligence. She realizes that she does not derive enjoyment where her contemporaries find it. In her desire to conform and to behave like the others (10 times k—) she may even try to emulate them; she will fail, and this will still more increase her unhappiness.

A comparison of the interpretation derived from the ego pictures will show that they agree with Rorschach and T.A.T. results.

Summarizing the main findings of the Szondi test, it seems that the patient is lacking in drive, that her sex life is on a childish level, that occasional hysterical outbursts may occur and that human relationship is erratic. She feels tense, unhappy and lonely, and will blame the environment for it. The underlying cause of the difficulties appears to be a constant shifting between male and female identification, which makes the patient unable to cope with reality in a satisfactory way and drives her into an autistic world of day-dreams.

Clinical Aspects.

In a thorough medical examination the conclusion was reached that the patient had a prolapsed disc in the lumbar region. She was, therefore, not a

suitable psychosomatic case for the Research Unit. In the meantime, however, she had revealed serious emotional difficulties, and she was kept in the Clinic for some time in the hope that it might be possible to readjust her.

Abstract of the Psychiatrist's Notes.

Mother died 1947. From this time forward the patient has been very depressed. Once tried to kill herself by taking a bottle of aspirin tablets. Patient is shy, timid, inhibited, anxious. Cannot speak of mother's death without weeping. While her mother was alive she had a certain amount of social life, but after her mother's death she found difficulty in making friends, and tended to behave in a solitary fashion. She has had several boy friends, but has not had sex experience. The father is described as being rather strict and ill-tempered. Patient remained much under mother's wing, and at her mother's death found herself completely helpless. She considers that she is misunderstood by her father, and she does not get on well with her sister. She is unhappy at home, but does not feel independent enough to leave home. The patient's difficulties are those of an immature personality who has never succeeded in forming a really satisfactory or mature relationship with either the mother or the father, and the precipitation of the condition is referable to the mother's death having aroused the conflict between her need for independence and maturity, and the more than normal degree of dependence.

Extracts from the Nurse's Notes.

23.i: . . . amiable, quiet and friendly during the evening. Hysterical outburst after supper, faintness, giddiness, feeling of complete hopelessness. Soon recovered, though very quiet and needing reassurance. Created a lot of emotional disturbance in the ward by a purposefully hurtful remark, apparently intended as a joke. Very difficult and hysterical till late last night.

24.i: . . . seems quite aware of the havoc she caused, but immediately broke down on being spoken to by Sister. Assumed an injured "nobody cares for me" attitude with frequent outbursts of tears. Shivering and depressed. . . . took 17 aspirins; told a nurse, but quite pleased about the fuss.

25.i: . . . quiet and constantly weeping in her bed, refused to be comforted.

1.ii: . . . quieter these days; most friendly to the other patients.

It was possible to give the patient some insight into her problems, her relationship with her father improved, and she was discharged feeling more able to cope with life.

Conclusions.

Case history and assessment by the psychiatrist confirm the personality picture derived from the tests and, moreover, the patient gradually exhibited in the ward the behaviour which the tests led one to expect.

The three tests revealed the same main features, illuminating them from different angles. As the material from which the conclusions are drawn is different for each test, each of them is able to contribute another facet to the

same piece of information. For instance, all three tests revealed suicidal tendencies. In the Rorschach test the inference was made from depressive trends and some morbid concepts which the test material had evoked. The T.A.T. test gave the concrete suicidal content, and the Szondi test showed the strength of the trend and the actual form it might take (p. 559). In the life situation the mental preoccupation which Rorschach test and T.A.T. had reflected led to action. The patient took 17 aspirins, but was careful to inform the nurse and seemed " to enjoy the fuss about it." The lack of seriousness of the attempted suicide and the hysterical exhibitionist form which any attempt might take had been correctly assessed by the Szondi test. In the present case the specific contributions of the Szondi test appear to have been twofold. It seems to have revealed the strength of the postulated drives in relation to each other, and to have provided some indication as to their level of integration.

Summary.

The genetic hypothesis on which the test rests is briefly stated, together with Szondi's schema of drives. Test material, administration of the test, the main types of reactions and the scoring are described. One clinical case is presented. Excerpts from the results of Rorschach test and T.A.T. and the complete results of the Szondi test are given. They are analysed and compared with the results of the two other projective tests. Finally, abstracts from the notes of the psychiatrist and of the nurse in charge of the patient are quoted. The test results are found to agree with them.

Undoubtedly, one case does not prove the validity and reliability of the Szondi test, but the results obtained in this case and in other cases would appear to justify more widespread investigations.

Gratitude is gladly expressed to Dr. T. A. Munro for permission to use the case-material, and to Dr. D. O'Neill and Dr. Charlotte Spitz for constructive criticism.

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EVALUATION OF ELECTRIC CONVULSION THERAPY AS COMPARED WITH CONSERVATIVE METHODS OF TREATMENT IN DEPRESSIVE STATES.

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In an article under the above title (*J. Ment. Sci.*, 1950, **96**, 1060–91) S. Karagulla compared the results obtained in six groups of patients. Two groups, male and female, had been treated at the Royal Edinburgh Hospital for Mental and Nervous Disorders in the years 1900–39, before electric convulsion therapy had come into general use. The remaining four groups had been treated in the years 1940–48, two, male and female, by electric convulsion therapy, and two, male and female, by conservative measures only. The author had the advice and encouragement of Professor Sir David Henderson, and the final statistical calculations were scrutinized by Professor A. C. Aitken. This background of authoritative support is mentioned here, because some readers may have felt that it lent to the author's arguments and conclusions an added weight.

As a result of her study of the comparative results obtained from the six groups the author concludes, among other things, that—

> "The percentage rate of recovery does not vary greatly whether patients are treated conservatively or with electric convulsion therapy. Such slight differences as may exist are statistically insignificant."

And—

> "It was found that the use of E.C.T. did not shorten the duration of hospitalization to any significant degree."

Both of these conclusions have, no doubt, been found surprising by clinicians with experience of E.C.T., and it is therefore desirable to examine the evidence rather carefully. If E.C.T. is of no avail, and the author's summarized results disclose no advantage in its use, then to give the treatment at all in states of depression would seem to be unjustifiable. The author herself does not draw this conclusion.

The two groups treated in the years 1900–39 are designated MC1 and FC1; the patients treated conservatively in the 1940–48 period are designated MC2 and FC2; and the patients treated by electric shock in the same later time are designated MT and FT, M and F in each case standing for male and female. From the author's Tables I and II the following facts may be abstracted (Table I):

Table I.

	Percentage of—					
	MC1.	MC2.	MT.	FC1.	FC2.	FT
Recovered	39·3	30·2	50·0	46·8	39·3	56·4
Improved	36·5	36·3	36·7	30·9	30·2	26·8
Not improved	8·3	15·4	11·2	8·7	20·6	15·4
Died	15·9	18·1	2·1	13·6	9·9	1·4

This table shows three features of interest. By far the most striking is the great difference in mortality between the treated and the untreated groups. The proportion of persons who died in the untreated groups is about eight times as great as the proportion of those who died in the treated groups. Secondly, the proportion of recoveries is substantially higher in the treated groups than in the untreated. Thirdly, the proportion of the unimproved is substantially lower in both groups of patients admitted during the years 1900–39. None of these points are mentioned by the author in her summary ; and readers who only read the summary, affrighted by the mass of tables and diagrams in the body of the paper, might never notice them.

The third feature might be considered first, as it is of relatively little interest. The 1900–39 groups have, of course, been under observation for a longer time than the patients admitted in the years 1940 to 1948. It is probable that, if there are fewer among them who have failed to improve, this is simply because of the greater lapse of time allowed for improvement to occur.

The other two features of the table which have been mentioned, the higher recovery rates and the lower death rates in the treated groups, are much more important. The author obscures both of them by a statistical device. She recalculates the percentage of patients recovered, improved and not improved in all six groups *after all deaths have been omitted*, and then shows that the advantage in outlook enjoyed by the treated patients when compared to the others disappears.

The author justifies this unusual procedure by the comment, " all deaths were excluded from the final statistical analysis because death, unless in the form of suicide, cannot be attributed to the depressive process. Depression *per se* is not a direct causative factor in mortality." One may pertinently inquire, to what cause then are attributed the deaths of those 177 patients in the four control groups who died ? Apart from the sprinkling of suicides, were none of them due to exhaustion or intercurrent infection, or to other causes which would never have arisen if the patient had not been mentally ill ? It is, however, not legitimate to exclude these deaths, whatever their cause, from a statistical analysis. They occurred, and their occurrence is clearly a risk attached to leaving depressive patients untreated by E.C.T. A clinical finding which has often been observed and reported is confirmed on a grand scale.

We now have to examine the author's conclusion that E.C.T. is without effect on the length of hospitalization. The relevant tables, given for the first hospitalization only, are shown on pages 1076–78, and the figures showing the percentage of patients discharged " recovered " within two months of admission are quoted below (Table II) :

TABLE II.

	Percentage of—					
	MC1.	MC2.	MT.	FC1.	FC2.	FT.
Recovered	9·4	25·8	3·9	9·7	21·7	9·7

The treated groups are at a disadvantage when compared with the untreated groups, particularly when compared with MC2 and FC2. We note, however,

that the really big differences lie between the second control groups, MC2 and FC2, and all others. The patients who were admitted during the years 1940–48 and not treated by E.C.T. do quite startlingly better than either the patients who were admitted during the same years and so treated, or those who were admitted during previous years and not treated.

Far from offering an explanation, the author does not comment on these differences at all. The explanation, however, is not far to seek, and may be set out as follows:

During the years 1900–39 all patients were handled in the same way, and E.C.T. was not used. After 1940, however, this treatment was available, and could be applied if the indications existed. The most important of these indications would be the continuing illness of the patient. If, before treatment was begun, the patient recovered or even looked like recovering, the indication for E.C.T. would be abolished or lessened. We note from the author's Tables VIII and IX that considerable periods elapsed between admission and the beginning of treatment. The period might even be as long as two years, and seems to have averaged about four months. Any patient, therefore, who was admitted to hospital during the years 1940–48 and rapidly recovered would automatically appear in the control groups, and be automatically excluded from the treated groups. This is the obvious explanation of the improbably high early recovery rates in the C2 groups. The treated groups, on the other hand, represent *ab initio* a selection in favour of cases with long duration. The selection has two separate effects: first, a period of non-recovery is arithmetically added to the duration of hospitalization of every treated case, thus biasing the statistics and rendering Karagulla's conclusion invalid; secondly, the treated patients are likely to represent the prognostically less favourable material, and are not therefore fairly compared with the other groups, even if, by search of individual records, an appropriate allowance were made in respect of the first error.

There appears to be only one valid comparison which might be made, and even to this there would be some objections, i.e., to take the MC2 and MT groups together, and compare the summed material with MC1, and to do likewise with the females. This would be a comparison of the results obtained in the pre- and post-shock eras, and would almost certainly establish the fact that greater therapeutic success was obtained at the later time.

Summary and Conclusions.

The statistical data provided by Karagulla in her paper of October, 1950, in this Journal do not justify two of her main conclusions, which were that electric convulsion therapy is without effect either on the recovery rate or on the duration of hospitalization in depressive states. A more careful examination of the data suggests that the exact contraries of both propositions are correct.

SUB-ACUTE SCLEROSING LEUCO-ENCEPHALITIS: A CLINICAL AND PATHOLOGICAL REPORT OF TWO CASES

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The first object of this paper is to describe the clinical and pathological features of two cases of sub-acute sclerosing leuco-encephalitis (first distinguished by van Bogaert in 1945). A second object is to compare these features with those of the Dawson inclusion type of sub-acute encephalitis (Dawson, 1933, 1934; Brain, Greenfield and Russell, 1943, 1948; Greenfield, 1950; Malamud, Haymaker and Pinkerton, 1950), and the final object is to emphasize the importance of mental change, when associated with motor symptoms, in the diagnosis of both these forms of encephalitis.

Case 1.—J. D—, a girl, 18½ years old at the onset of the illness. There was no history of nervous or mental abnormality in either the parents, siblings or near relatives.

Previous history.—A full-term baby, forceps delivery. At the age of 3 years she became unsteady on her feet, but recovered completely within a few weeks. When 4 years old she had whooping-cough and pneumonia, and at 17½ years she suffered from a febrile attack described as influenza. There was no history of recent inoculation or vaccination.

She was a normal child and an average scholar. From the age of 14 to 17 she was at work, mainly as a shop assistant, and during this period she changed her job at progressively shorter intervals. Finally she stayed at home for a year to help in the house, but shortly before the onset of her first symptoms she was planning to leave again.

Present illness.—In October, 1946, 10 weeks before admission to the Maudsley Hospital, she noticed that her right hand would jerk when she tried to pick anything up and shortly afterwards she began to stumble. To other people at this time she appeared jumpy and occasionally vacant. A week later her right leg began to jerk spontaneously about once a minute and the physician to whom she was referred made a tentative diagnosis of hysteria.

During the next few weeks the spasms developed in her neck muscles and attacks of spinal hyper-extension caused her to fall continually. At the same time her left arm started to jerk and, although her right leg improved, the right arm became worse. Shortly before admission her speech became slurred and her shoulders began to droop.

Parallel with the development of these physical symptoms her mental state rapidly deteriorated. The slight listlessness and the vacancy noticed at first gave way to a more stupid expression and to frequent giggling. She could often talk sensibly, usually in answer to questions, but she could not solve any simple problem. Within a few weeks she was unable to feed or dress herself, although she could still express herself sufficiently to complain of severe headache and of being kept awake by the spasms.

When admitted on 31.xii.46 she appeared pale but not markedly ill or wasted. She showed little spontaneous activity apart from the jerking movements. Her mental state was one of extremely rapid fluctuation alternating from confusion with impairment of concentration, attention and memory to one of relative lucidity with correct orientation and a moderate degree of insight. In answering questions she often perseverated and would confabulate readily; there was occasional blockings. Her mood would quickly change but was more often one of depression than of cheerfulness.

Physical examination.—Significant findings were confined to the nervous system

and of them the most striking were the involuntary movements. These occurred about once a minute but were irregular in rate and rhythm and consisted of a not very rapid flexion of the elbows and wrists with pronation of the forearms; at the same time there was slight flexion of the knees, elevation of the shoulders and opening of the mouth and eyes. The contractions would last for a few seconds and then pass off. Although occasionally precipitated by a loud noise, they were not markedly affected by outside stimuli and they stopped during sleep.

Power in voluntary extension of the limbs was slightly reduced. Extrapyramidal rigidity was present throughout, and was most marked in the left arm. Sustained ankle clonus was elicited on the left side but was not present constantly. Tendon reflexes were normal. The patient was unable to stand without falling backwards and could not walk without help. She then walked on a narrow base using short steps and held her back hyper-extended. No other signs of inco-ordination were present and no sensory abnormality was detectable. There was slight bilateral ptosis; otherwise the cranial nerves and the fundi were normal.

Progress.—A fortnight after admission a low-grade evening pyrexia (occasionally up to 101° F.) started and this continued intermittently until death. Gradually the rigidity of the upper limbs increased and the spasms became as frequent as three to four a minute. They changed to a predominantly extensor type and included torsion movements of the head and neck. Voluntary movements were extremely limited and the wrists and ankles were firmly flexed. The patient lay sweating profusely, with her head retracted to the left, her right arm at her side with the elbow rigidly extended and the left arm across her chest; her pupils were widely dilated. Swallowing and talking were very difficult, she became progressively drowsier and would only grunt if questioned. Twelve weeks after admission, and about five and a half months after the onset, she died in coma with a terminal hyperpyrexia of 106° F.

Laboratory investigations—On two occasions (26.xi.46 and 17.xii.46) the Wassermann reaction was negative in the blood, but on the same specimens the Kahn was strongly positive (+++).

The cerebro-spinal fluid was first examined on 4.i.47 and then at approximately three-weekly intervals and on each occasion the most striking abnormality was the presence of a paretic colloidal gold curve (5554321000). On one occasion (28.i.47) the cell count rose to 10 per c.mm. with a protein content of 20 mg./100 c.c., and on the last, twenty-four hours before death, the cell count was 7 with a protein content of 50 mg. All other findings, including the pressure and chloride levels, were normal and the five Wassermann reactions were consistently negative.

With the exception of a white cell count of 10,400 per c.mm. (polymorphs. 65 per cent., lymphocytes 30 per cent.) on 10.i.47, the blood picture on three occasions was normal. The E.S.R. (Westergren) varied from 4 mm. in the first hour (on 20.i.47) to 20 mm. (on 13.i.47 and 1.ii.47).

Electro-encephalogram (Dr. Denis Hill).—Three recordings were taken over a period of eleven weeks, the first being on 4.xii.46 and the last on 25.ii.47. They constitute a series showing progressive and recognizable changes. There is first the disorganization and final disappearance of the normal alpha rhythms in the occipital areas. Secondly, there is the finding of greater slow wave activity in the left post-central areas, which becomes progressively more apparent. Thirdly there is the unusual appearance of paroxysmal slow wave activity of high voltage, which is at first episodic and finally periodic with a frequency incidence of approximately ten per minute. This corresponds with the frequency of the involuntary movements which occur *at the end* or *immediately after* the cortical discharge. This is in contrast to that which normally occurs in epilepsy, in which the motor activity coincides with the electrical cortical discharges. A full report and discussion of the findings is being published (Cobb and Hill, in press).

Post-mortem examination.—Autopsy, performed 14 hours after death, revealed the body of a moderately nourished girl. Apart from slight broncho-pneumonic changes in both lung bases, abnormal findings were restricted to the central nervous system.

The skull, dural sinuses and dura mater were normal in appearance. There was moderate diffuse injection of the pial vessels, slightly more intense posteriorly and especially over the left parieto-occipital region. The uncut brain showed no abnormality and, apart from slight injection of the pial vessels, the spinal cord appeared normal.

The brain weight, after 10 days' fixation in 10 per cent. formalin, was 1410 g. Coronal section at the level of the infundibulum showed a diffuse injection of the small vessels of the white matter. The substantia nigra appeared normal.

Microscopical examination.—Celloidin blocks were prepared from representative areas of the frontal, parietal, occipital and temporal lobes, the hippocampus, the basal ganglia, mid-brain, pons, cerebellum, medulla and the cord at the 5th cervical level. Sections were stained by Nissl, van Gieson, and by Holzer methods; by Turnbull's method for iron, by Heidenhain's method for myelin and by Lendrum's phloxin tartrazine method for inclusion bodies. Frozen sections were stained for fat, astrocytes, neurofibrils and microglia (Herxheimer, Hortega, Bielschowsky and Penfield methods respectively).

FIG. 1 (Case 1).—Cortex and particularly white matter of the left occipital lobe showing marked perivascular infiltration. There is also mild meningeal infiltration and increased cellularity of the cortex. Cresyl violet. × 20.

Meninges.—The leptomeninges showed slight fibrous thickening and a moderate infiltration with lymphocytes. In those areas overlying severe cortical involvement perivascular infiltration of the pial vessels with both lymphocytes and plasma cells was especially marked, most noticeably within the sulci.

Cortex and subjacent white matter.—All areas of the cortex and subjacent white matter were affected to a greater or lesser degree, the most severe changes being in the central region. Here there was gross perivascular infiltration of both small and large vessels with lymphocytes and plasma cells, the vessels of the white matter being more involved than those of the cortex. Microglial proliferation with the formation of many rod cells, was noticeable in all cortical layers while the proliferation of astrocytes was mainly concentrated in the deeper layers and in the underlying white matter. The lamination of the cortex was largely obscured by this increase of glial cells; there appeared to be a generalized loss of nerve cells especially in the third layer while those remaining showed "severe" degenerative changes, the latter resulting in extreme cases in the appearance of ghost cells.

The occipital region (Fig. 1) was the next most severely affected area, the lesions being most noticeable on the dorso-lateral surface whereas the striate area was relatively spared. Although loss of neurons was less marked than in the central area both the cell changes and the glial reaction appeared equally severe. The frontal, parietal and temporal lobes were all moderately affected ; there was some loss of pyramidal cells in the hippocampus.

FIG. 2 (Case 1).—Holzer preparation showing glial fibrosis in the white matter. Frontal lobe. × 3.

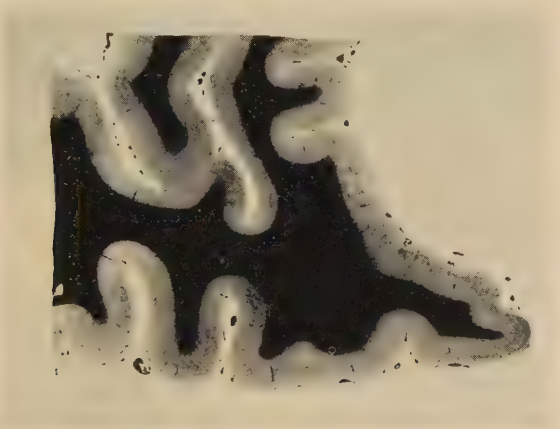

FIG. 3 (Case 1).—Heidenhain preparation for myelin, showing absence of demyelination. Frontal lobe. × 3.

Throughout the white matter there was a patchy but formidable glial fibrosis (Fig. 2), although there was no evidence of myelin breakdown in Heidenhain preparations (Fig. 3.).

Thalamus.—Considerable cuffing and glial proliferation were present with the formation of glial nodules. These changes were most severe in the anterior nucleus and to a lesser extent in the nucleus lateralis posterior and the dorso-medial nucleus.

Corpus striatum.—The striatum was less severely affected than the thalamus although there was a moderate loss of small nerve cells ; the pallidum was least

affected of all. The blood vessels in and around the claustrum showed the severest cuffing seen at subcortical levels.

Hypothalamus.—The anterior hypothalamus was intact while the mammillary bodies showed slight glial proliferation and cuffing of vessels with lymphocytes. At this level the medial third of the subthalamic nucleus was similarly affected.

Mid-brain.—There were some inflammatory changes in the substantia nigra, but they were moderate compared with the more severe infiltration in the cerebral peduncles (Fig. 4). There was no loss of melanin in the nerve cells of the substantia nigra.

FIG. 4 (Case 1).—Midbrain showing inflammatory changes in substantia nigra and—more marked—in the cerebral peduncle. Cresyl violet. × 20.

Pons.—The dorsal part was not appreciably affected but ventrally much perivascular cuffing. with the formation of glial nodules, was scattered throughout the pontine nuclei, a moderate number of nerve cells showed degenerative changes.

Medulla.—Very slight cuffing with slight glial proliferation was apparent in both olives.

The cerebellum and the spinal cord both appeared normal. The iron reaction was negative throughout. An extensive search for inclusion bodies was made but none was found.

CASE 2.—I. C—, a girl, was 20½ years old at the onset of the illness. She had been admitted in December, 1945, to St. Lawrence's Hospital, Caterham, and was described as a low-grade imbecile.

Present illness.—During the first few days of April, 1947, the patient became unsteady on her legs and within three weeks was unable to walk without considerable help. At the same time it was noticed that she talked much less than usual and that she no longer answered questions.

Physical examination.—On examination on 18.iv.47 she did not appear to be markedly wasted and there was no pyrexia, although her pulse rate was increased.

She was unable to sit up without falling over. There were no abnormal movements, her left arm was held firmly flexed. There was some weakness of grip in the right hand with slight wasting of the hypothenar muscles and movements of both feet were weak in dorsiflexion. The left arm and right leg were moderately spastic and their tendon reflexes, in general, were greatly increased, whereas the tendon reflexes of the other limbs were only slightly so. Abdominal reflexes were absent on both sides; the plantar responses were both flexor.

If given enough support she could just walk but then only on her toes with her knees bent and with a marked tendency to fall to the right. An intention tremor was present in both upper limbs. The cranial nerves were normal and no sensory changes were recorded.

Progress.—A week later, on 25.iv.47, the patient developed an irregular pyrexia reaching 103° F., but without signs of a localized infection. This was followed within a few days by a tremor of the head and arms, more marked on the left. Movements of her spine, but not of her neck became restricted and the spasticity of the left arm and right leg increased.

At this stage she was no duller or more confused than at the previous examination but it was noticed on 30.iv.47 that the area level in her cerebro-spinal fluid was 171/mg. 100 c.c. and on 2.v.47, when the blood urea was 380 mg./100 c.c. she started to become drowsy. At the same time, in addition to the tremor of the arms, she developed choreiform movements of the neck (in neither of these did the movements stop during sleep). There was a white cell count of 19,200 per c.mm. with 77 per cent. polymorphs. and 21 per cent. lymphocytes.

By the following day she was stuporose, lying with her eyes closed, her arms on her chest, her fists clenched and her knees slightly flexed. Her head rocked from side to side and at times there were agitated movements of her arms, usually spontaneous but which could be precipitated by attempting to move her legs. The spasticity of her limbs was further increased, especially on the left side.

The protein level in the cerebro-spinal fluid had risen by this time from normal (on 21.iv.47) to 80 mg./100 c.c. with no cells, and two days later, on 5.v.47, the blood urea reached 685 mg./100 c.c. A slight squint was then noticed, the right leg became flaccid and the knee-jerk absent. The patient died three days later, (8.v.47) the blood urea having reached a concentration of 1050mg./100 c.c. the day before death.

Laboratory investigations.—On admission in 1945 the blood Wassermann reaction had been negative and it was again negative on 21.iv.47.

The cerebrospinal fluid was examined three times during the disease, the most striking finding being a strongly paretic colloidal gold curve:

	21.iv.47.	30.iv.47.	4.v.47.
Pressure	Normal	Normal	Normal
Cells	*Nil*	1 lymph/c.mm.	*Nil*
Protein	30 mg./100 c.c.	Positive Pandy	80 mg./100 c.c.
Sugar	90 mg./100 c.c.	78 mg./100 c.c.	—
Chlorides	625 mg./100c.c.	885 mg./100 c.c.	—
Colloidal gold curve	5554321000	5555554321	—
Wassermann	Negative	Negative	Negative

No E.E.G. recordings were made.

Post-mortem examination.—The body appeared to be moderately nourished. No gross abnormality was found in the viscera and a report on the kidneys from Dr. M. K. Beattie, of the Mental Hospitals Group Laboratory, Epsom, stated that "macroscopically they appear normal; microscopy shows congestion of the intertubular capillaries. The glomeruli appear normal. The main features are cloudy swelling of the convoluted tubules and some interstitial oedema. The high blood urea would appear to be primarily extra-renal in origin."

The brain after fixation in 10 per cent. formalin weighed 1050 g. There was marked congestion of the pial vessels but otherwise the surface appeared normal. Coronal section through the frontal and occipital lobes showed the white matter to be soft and slightly grey; section at intermediate levels showed these changes less distinctly and only in patches. There was slight enlargement of the third and lateral ventricles, especially the posterior horns. The substantia nigra was poorly pigmented.

Microscopical examination.—Sections were prepared as in Case 1.

Meninges, cortex and subjacent white matter.—There was slight diffuse infiltration of the leptomeninges mainly with plasma cells, perivascular cuffing being less marked than in the first case.

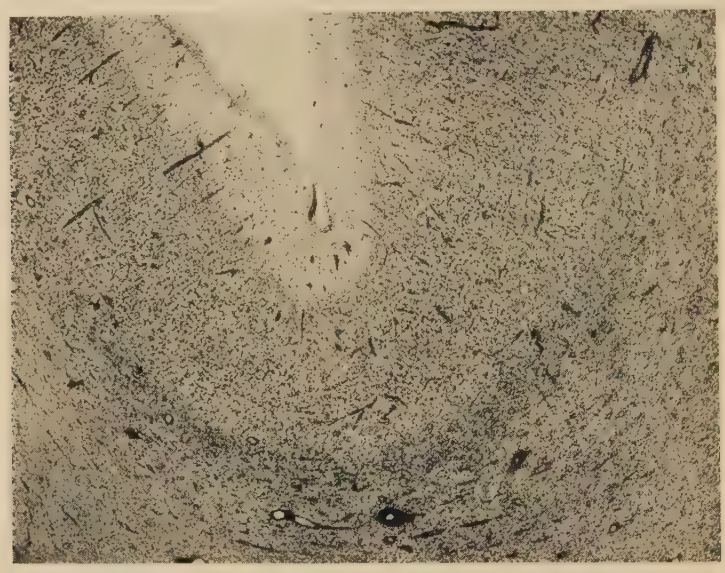

FIG. 5 (Case 2).—Cortex and white matter of left central sulcus showing perivascular infiltration, especially of the larger vessels. The cortex also shows marked glial proliferation. Cresyl violet. × 20.

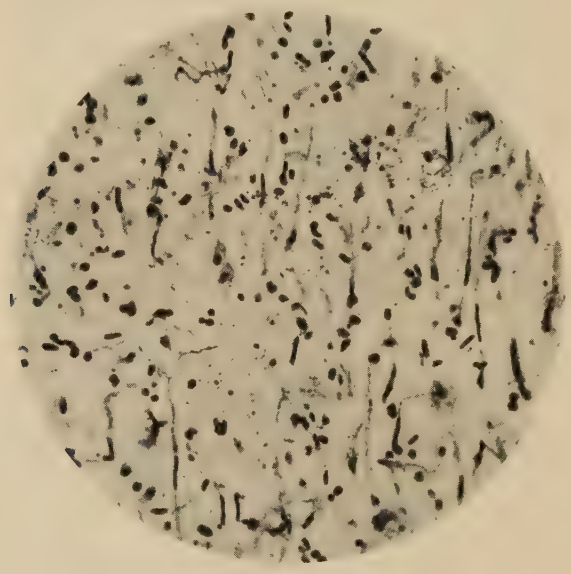

FIG. 6 (Case 2).—Microglial proliferation in the cortex. Penfield stain. × 250.

The most severely affected area of cortex was in and around the central sulcus at the vertex (Fig. 5) while in the occipital, frontal, temporal and parietal lobes the changes were progressively less marked.

Nerve cell changes were generally less severe than in the first case although there

FIG. 7 (Case 2).—Heidenhain myelin stain showing a small patch of demyelination in the left occipital lobe. × 1·7.

FIG. 8 (Case 2).—Holzer stain showing dense glial fibrosis corresponding to the demyelinated area in fig. 7. × 1·7.

appeared to be a considerable outfall in patches and a high proportion of the remaining cells showed swelling and chromatolysis while the bodies of others appeared shrunken. In Bielschowsky preparations a number of cortical nerve cells showed varying degrees of Alzheimer's neurofibrillar change (Figs. 11 and 12) although this was not found at other levels. The glial proliferation was striking and a large number of astrocytes could be seen in the deeper layers of the cortex and subcortical white matter, while proliferated microglia, in the form of rod cells, were prominent throughout the cortex of all areas examined (Fig. 6.).

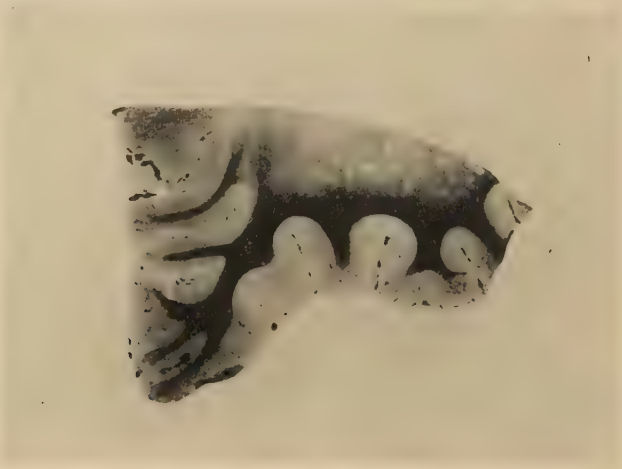

FIG. 9 (Case 2).—Heidenhain stain showing demyelination in left frontal lobe. × 1·7.

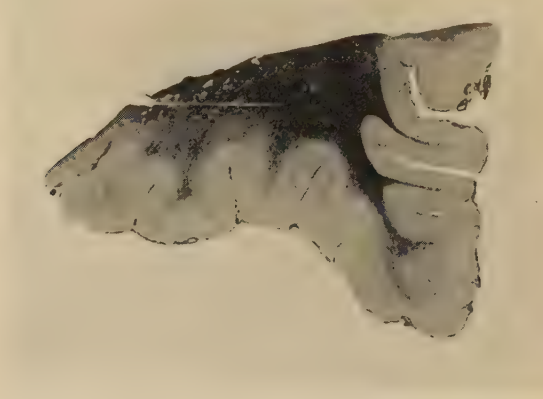

FIG. 10 (Case 2).—Holzer stain showing glial fibrosis in the left frontal lobe. × 1·7.

The changes in the white matter were considerably more marked in this case and in addition to a moderate inflammatory reaction, patches of demyelination were present throughout the hemispheres. These were particularly noticeable in the subcortical region and appeared to be of moderate size, with poorly defined edges and tending to coalesce (Figs. 7 and 9). Within these areas of myelin breakdown a moderate number of compound granular cells was found which contained coarsely granular anisotropic lipoid material staining brightly with Scharlach R. Many axis cylinders appeared swollen and beaded. Also corresponding to the areas of demyelination but spreading beyond them was a dense glial fibrosis (Figs. 8 and 10). Of the areas examined these changes were most marked in the occipital lobe (Figs.

7 and 8), but were also present to a lesser degree in the frontal (Figs. 9 and 10) and temporal lobes.

Basal ganglia and hypothalamus.—With the exception of the striatum, which was only moderately affected, the perivascular reaction was very severe at this level—the pallidum, the thalamus and hypothalamus all being markedly infiltrated both with plasma cells and with microglia, the latter sometimes forming nodules. Nerve cell changes were similar in intensity to those in the cortex.

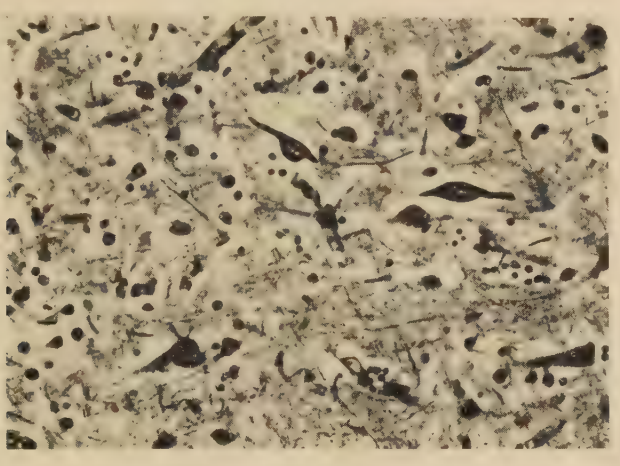

FIG. 11 (Case 2).—Low power view of three nerve cells showing Alzheimer's neurofibrillar change. Bielschowsky stain.

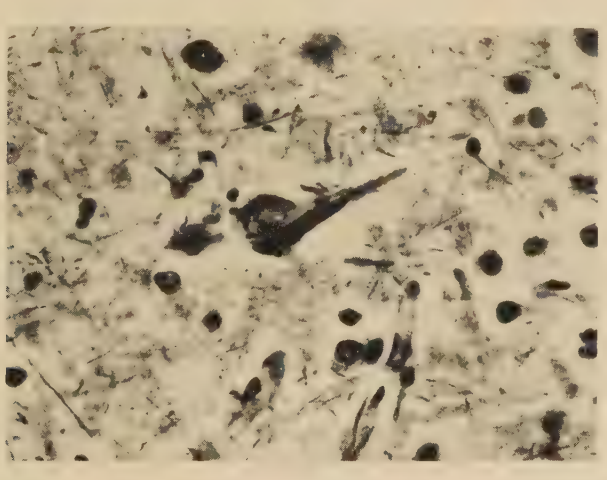

FIG. 12 (Case 2).—High-power view of nerve cell showing early neurofibrillar change with a relatively intact nucleus. Bielschowsky stain.

Mid-brain.—At this level the pathological process was becoming less marked, although the tectum, red nucleus and cerebral peduncles were moderately affected. The cells of the substantia nigra appeared to be fewer than normal and those remaining were shrunken and contained little pigment.

Pons.—The perivascular reaction was still noticeable, the vessels of the pontine nuclei, however, being considerably more affected than those of the dorsal part. Also scattered through the pontine nuclei were a few small glial nodules, but there did not appear to be any appreciable glial fibrosis.

Cerebellum.—The only part to be involved was the dentate nucleus which showed very slight cuffing of the vessels and a small amount of microglial proliferation.

Medulla and cord.—In the medulla the changes were similar to, but less marked than, those in the pons, the inferior olives containing an occasional glial nodule and a small amount of perivascular cuffing. The spinal cord appeared normal.

The iron reaction was negative throughout. As in the first case an extensive search for inclusion bodies was without result.

Discussion.

The *clinical* picture drawn by van Bogaert for sub-acute sclerosing leuco-encephalitis is that of a disease fatal in three to six months. It is characterized by the rapid development of a severe dementia concurrent with the onset of involuntary motor activity, ranging from myoclonic spasms to choreo-athetoid movements, and ending in a state resembling decorticate rigidity. There is usually marked wasting and there may be a mild pyrexia with a leucocytosis.

In both cases described in this paper the clinical picture is very similar to this, although in Case 2 the development of mental deterioration would be obscured by the defect already present and the terminal stages, moreover, were complicated and probably accelerated by the onset of uraemia. As already mentioned, microscopical examination of the kidneys threw no light on the cause of the uraemia and this complication is therefore unexplained. At the same time it is possible that the findings by Cumings (1942) of a raised blood urea in patients with severe head injury may be related. The presence of the uraemia may help to account for the unusual shortness of the illness when considered in conjunction with the improbability of detecting early symptoms in such a patient.

The first case developed typically, even to the onset of motor symptoms on the right side—a characteristic noted by van Bogaert. In this connection it is also interesting to recall the predominance of E.E.G. changes on the left side. The positive Kahn reaction in the blood does not justify a diagnosis of syphilis in view of the repeatedly negative Wassermann reaction in both blood and cerebrospinal fluid, and also in view of the subsequent histological findings. In both cases there was an intermittent pyrexia and in the second, a leucocytosis. In neither case would the wasting appear to have been as extreme as that described by van Bogaert.

With regard to the cerebrospinal fluid, although van Bogaert maintained that no typical changes are present, it is now seen, as pointed out by Greenfield (1950), that in five of the six cases in which a colloidal gold or similar reaction has been done the result has been a paretic curve (Bodechtel and Guttmann, 1931 ; cases 1 and 3 of van Bogaert, 1945 ; case 14, Greenfield, 1950 ; and the two cases presented here). It might also be mentioned that in sub-acute (Dawson type) encephalitis, of the six cases with a curve recorded all were paretic (Akelaitis and Zeldis, 1942 ; Brain, Greenfield and Russell, 1948 ; Greenfield, 1950 ; Malamud, Haymaker and Pinkerton, 1950), as it was in the third case of chronic encephalitis described by Rosanoff (1947).

In the present cases, as in the nine others previously described (Bodechtel and Guttmann, 1931 ; van Bogaert and de Busscher, 1939 ; van Bogaert, 1945 ; Rosanoff, 1947 ; Dubois, van Bogaert and Lhermitte, 1949 ; Greenfield, 1950), it is impossible to ignore their clinical resemblance to other types of sub-acute encephalitis, and especially to the Dawson type. In this the clinical picture,

as described by Brain *et al.* (1948), is that of an illness of children, fatal in nine weeks to six months, characterized by progressive dementia and, in three cases out of four, by myoclonic movements of the limbs and face, the ultimate picture being one of decortication. Moreover, the three cases of Malamud *et al.*, the two cases described by Dawson and the one by Akelaitis and Zeldis had a similar picture. Throughout all the descriptions such expressions as " involuntary jerking movements," " hyperkinetic seizures, like torsion spasms," " large flexion athetotic movements," occur, while in association with them are a variety of mental changes similar to those found in sub-acute sclerosing leuco-encephalitis. Since the majority of cases in both types of encephalitis are children these changes usually make their appearance as a fairly sudden failure of school work. The child becomes forgetful and slovenly and his attention wanders. There is either emotional blunting or increased lability, and even if no involuntary movements are manifest at this stage, there is nevertheless a generalized clumsiness of behaviour.

The main *histological* features of van Bogaert's encephalitis are the presence throughout the hemispheres and brain stem of an inflammatory reaction together with glial proliferation in both grey and white matter, but predominantly in the latter where it results in glial fibrosis out of proportion to the myelin damage since that is either absent or, if present, is usually slight.

Both the cases just described correspond sufficiently closely to this to suggest a diagnosis of sub-acute sclerosing leuco-encephalitis. Case 1 is in all respects typical and, apart from the serology already discussed, fits into this diagnosis equally exactly from the clinical point of view. Case 2, from the histological aspect, is aberrant in that the demyelination is more marked than usual, but nevertheless it would not appear to be greater than that in the case described by van Bogaert and de Busscher, while the severe generalized inflammatory reaction would rule out the diagnosis of a primarily demyelinating disease.

In connection with histological classification van Bogaert finally decided that his cases belonged " parmi les encéphalites vraies de substance blanche ou ayant une prédilection marquée pour la substance blanche," and accordingly grouped them with post-infective leuco-encephalitis and the acute haemorrhagic leuco-encephalitis of Hurst. Greenfield (1947), while emphasizing that the nosological position was uncertain, provisionally classified them in the group : " Encephalitis affecting both grey and white matter," while more recently (1950) he suggested the title of sub-acute sclerosing pan-encephalitis in order to lay more stress on the changes in the grey matter. Malamud *et al.* made a similar recommendation and certainly the two present cases would seem to support this view for, although in many parts of the white matter the perivascular reaction is outstanding, at the same time the cortex is by no means spared. Moreover, there is considerable widespread nerve cell degeneration and glial proliferation both in the cortex and in the subcortical grey matter to an extent that would not easily be accounted for by a primary involvement of the white matter.

With regard to the relation of the Dawson and the van Bogaert types of encephalitis, little can be said, for while they are, as just mentioned, clinically alike, they nevertheless appear to differ histologically in that the former is

characterized by the presence of inclusion bodies and by the predominant involvement of the grey matter with relative integrity of the white. In addition the neuronal necrosis may possibly be more severe than in the van Bogaert type. On the other hand, failure to detect inclusion bodies may be due to technical factors or to an insufficiently intense search rather than to their absence, although in regard to the latter, Dr. J. G. Greenfield, who kindly examined a number of preparations of both cases, confirmed their absence. In any case, their existence represents a variation of the reaction of the host and does not necessarily specify the exact nature of the harmful agent. Whether the clinical similarity is therefore due simply to the diffuse and sub-acute nature of the inflammatory process or whether there is in fact any closer relationship, in spite of the *apparent* histological differences, must depend on virus or allied studies and cannot be fruitfully discussed here.

One point of interest in the second case was the presence of Alzheimer's neurofibrillar change in a small number of cortical nerve cells although this was not found at other levels. A similar change, but present in both cortex and brain stem and originally observed in chronic epidemic encephalitis by Hallervorden (1933), was described by Malamud *et al.* in their third case of inclusion encephalitis—a girl ten years old at the onset of an illness lasting seven years. The present case was also young—twenty years old, but the apparent length of the illness was only five weeks. It is, however, possible that owing to the mental defect the real length was greater and in view of this doubt it would not seem to be a case from which any conclusions could be drawn.

Finally, it may be worth while to draw attention to the prominence of mental symptoms in these two forms of encephalitis since a number of the cases so far described, including the two present ones, were seen in mental hospitals. Moreover the case described by Rosanoff died in a mental hospital, and in two of the four cases described by Brain *et al.* the first symptoms were "psychological —a change in temperament." The first case of Malamud *et al.* gave the initial appearance of catatonic schizophrenia and one of van Bogaert's four cases presented as an affective psychosis, while two others were noticed to be deteriorating mentally before the onset of other symptoms became apparent.

Summary.

Two cases of sub-acute sclerosing leuco-encephalitis are described clinically and pathologically.

It is suggested that they support the view that while this type of encephalitis *apparently* differs histologically from that of Dawson, it is clinically very similar.

The prominence of mental symptoms in both these types of sub-acute encephalitis is stressed.

My thanks are due to the Medical Superintendent of St. Lawrence's Hospital, Caterham, and to Dr. W. W. Kay, Pathologist to the Mental Hospitals Group Laboratory, Epsom, for permission to use the clinical and post-mortem records of Case 2.

I am especially grateful to Dr. J. P. Crawford, who had previously studied these cases, for permission to make further use of his material. I am extremely

indebted to Professor Alfred Meyer, who suggested this investigation, and to Dr. Turner McLardy, Dr. A. L. Woolf and Mrs. E. Beck for their invaluable advice and criticism. I am further greatly indebted to Dr. J. G. Greenfield both for his examination of these cases in relation to the presence of inclusion bodies and also for his help and advice.

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SOME OBSERVATIONS ON NEUROSIS IN FARM ANIMALS.*

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It is important, at the outset, to define the purposes which can be served by studying the subject of neurosis in animals, and they appear to be twofold. Firstly, animals display emotions in a simplified form, because their behaviour is not influenced by social conventions, and thus one can sometimes recognize vital underlying human feelings which are masked by other less important habits. A simple example of this is seen when two animals are given identical meals in separate feeding dishes ; each animal is convinced that the other has a better meal, and they will not be happy till they have changed dishes : in human relationships, the feeling that the other person has something better often plays a major part in determining behaviour, but it is frequently disguised and seldom admitted by the person concerned. The second way in which animals can help in the study of human medicine is in controlled experimental work ; for instance, the relative effects of heredity and environment can be studied comparatively easily in animals, and although it is important to remember that arguments based on animal behaviour cannot be applied directly to human behaviour, much can be gained by an exchange of information between workers in the two fields.

This paper is essentially the result of observations made over a long period of time, and of information collected from people whose life has been devoted to looking after animals of many different species ; such people, whether they keep animals for pleasure or profit, usually have exceptionally good powers of observation, and a knowledge of animal behaviour which the mere scientist can never achieve through laboratory experiments. Certain terms, common to veterinary and human medicine, have slightly different meanings in the two subjects ; in this paper, which describes animal behaviour, the terms have been used in the veterinary sense.

There are three main points which will be considered :

(1) Forms of neurosis in animals.
(2) Possible causes.
(3) Treatment and future research.

Forms of neurosis.—The behaviour of cows has been studied extensively, because milk yield is an important item on every dairy farm ; cows vary enormously in their temperament, both from one individual to another and from one breed to another. Anxiety neurosis is commonly seen, and can be readily recognized by the fact that the cow will refuse to " let down " her milk ; a stranger in the cowshed at milking time may cause neurotic cows to give

* A paper read at the Quarterly Meeting of the Royal Medico-Psychological Association held at 11, Chandos Street, W.1, on 15 February, 1951.

almost no milk, although he does nothing more than stand in the door of the shed. "Let down" incidentally is an example of an easily-formed conditioned reflex, and stimuli such as music, or warm water on the udder, can be used very effectively. The correlation of physiognomy with neurotic temperament is very noticeable among the different breeds—the heavy South Devon cows are typically phlegmatic, while the more finely-drawn Ayrshires are prone to neurosis. Again, among bulls, neurosis is an important factor in the mating process; the presence of a stranger will often prevent a bull from mounting, and any disturbance in the established routine may cause the bull to become quite unmanageable.

Neurosis in horses can be readily recognized by the fact that the animal breaks out in a profuse sweat and often trembles all over, with widely dilated nostrils and wild staring eyes. This behaviour is more common among the lighter breeds, but instances of it occur among draught horses also. It is a far more difficult thing to rationalize than the neurosis of the cow, because it often occurs every time a horse passes a certain spot in the road, where, so far as is known, nothing alarming has ever occurred. The horse has a phenomenally long memory, and this may sometimes be the explanation, but there are definite cases recorded in which it is known that the horse has never been to the spot before.

The effect of the temperament of the human being on the behaviour of the animal is of course obvious in almost all species, but it is shown more definitely in the association between horse and rider (or driver) than anywhere else. A neurotic rider will reduce a normally calm horse to such a state of nervous tension that one can hardly believe it is the same animal—it seems to lose all power of reason; conversely, one can see the trembling of a nervous horse cease *as* a confident rider mounts.

Neurosis in goats may occur as an exaggerated sequel to a slight fright, or, very commonly, as a sequel to anger and frustration of will. A goat which had had a simple intra-muscular injection fell down and seemed paralysed on seeing the veterinary surgeon enter the stable some days later. Similarly, certain goats when led in the direction in which they do not want to go will fall down as if in an epileptic fit, but will recover at once if allowed to have their own way.

It is of some interest, from the point of view of human medicine, that abortion has profound psychological effects on a goat. The animal will bleat continuously for weeks after an abortion, in what can only be described as a hysterical manner, and nothing will comfort her (although in one case a kitten was given to the goat in place of its kid, with remarkably good results).

Hysteria in dogs is a well-recognized condition, and is becoming increasingly common, both among farm and pet dogs. The dog is usually stimulated by some unknown "trigger" and thereupon loses all reason, recognizing no one and running off howling wildly. Sometimes it runs in circles, but more commonly in a straight line, until exhausted; it then lies down still dazed, and gradually, in anything from 5–15 minutes, emerges from its stupor. As soon as it is fully conscious it is quite normal and there are no signs of hysteria until the next attack. Dogs are also subject to fits, similar to human

epileptic fits, and to meningitis and rabies, but these conditions are quite distinct from the neurotic hysteria.

Possible causes.—These can be considered under three main headings—heredity, environment and feeding. No doubt each of these factors can play a part, but there is strong evidence to suggest that heredity is the most important factor. This evidence consists of general observations, and of a particular experiment.

During the past 50 years in-breeding has been practised to an alarming extent in the dog-breeding world, and to a lesser extent among dairy cows and racehorses. The increase in hysteria and in a generally unstable temperament is obvious to anyone who has seen much of pedigree dogs during this period, but no similar increase is apparent among mongrels. It is significant that the society responsible for training dogs to lead blind people have had to reject 80 per cent. of the pure-bred Alsatians which they used to use for this work, and are now using first crosses from Labradors and Alsatians. They need dogs which can be relied upon not to become neurotic under the most trying circumstances, and find that the cross-bred animal is definitely more satisfactory.

Eight dogs have lived under identical conditions in my own home, and have been carefully observed throughout their lifetime ; the mongrels alone showed no neurotic symptoms. Whether neurosis appears when " hybrid vigour " is lost, or whether it is due to a recessive gene brought into action by in-breeding, is a question which only long-term genetical experiments can answer.

The experimental work on the relative effects of heredity and environment was carried out in a herd of dairy goats ; the environment and husbandry of the goats was identical in every case, and in the majority of the matings the male was the same animal. The kids did not suckle their dams, and during the day were in a separate " play-pen," but they did spend the nights with their dams when young.

The herd consisted initially of three goats of widely differing temperaments. No. 1 was a highly intelligent goat, easily upset and liable to attacks of extreme hysteria on the least provocation ; she was the natural leader of the herd. No. 2 was a calmer goat with less intelligence than No. 1, fond of human beings and greedy ; she seldom showed hysterical symptoms except when frustrated, and then she would become rigid. No. 3 was a very peaceful animal, anxious to cause no one any trouble. The children and grandchildren of these three goats have now been reared. The offspring of No. 1 showed all her intelligence and all her neurosis ; her daughter screamed for weeks after an abortion, and her granddaughter shivered and shook during the whole of a 20-mile car journey when every other kid had settled down and started to eat hay after a few miles. The children of No. 2 have inherited her need for human companionship, her greed and her hysterical rigidity when their will is frustrated—her daughter shows this in an exaggerated form, falling down as if in a fit. Finally the children of No. 3 are placid animals, undisturbed by changes in routine and showing no neurosis.

Environment, no doubt, plays some part in the production of neurosis, but it seems to be a minor one superimposed on the basic hereditary make-up of the animal. The interplay between the human being's temperament and the

animal must have some bearing on the appearance of neurosis. Pavlov's classical experiments on the production of neurosis in dogs by the presentation of increasingly difficult problems have been confirmed in the field on one or two occasions. A pack of hounds which was watched over a period of years occasionally had widespread outbreaks of hysteria; these attacks always occurred at a check, when scent was poor, and the brains of the hounds presumably were severely taxed.

The feeding experiments of Mellanby and others do indicate that both fits and hysteria can be produced by toxic factors in agenized flour, but it is doubtful if this factor operates in practice, because there are so many instances of only one animal showing neurosis in a group having an identical diet. The vitamin B complex has been considered important by some workers, but again it appears to have little therapeutic value in established cases of neurosis. One case of canine hysteria responded well to parathyroid extract, but this was an isolated case and numerous other dogs have failed to respond.

Some years ago a thesis was written showing that dogs contract hysteria from sniffing the urine of dogs which are hysterical. This theory was subsequently ridiculed, but recently we have realized that Leptospira canicola is contracted in just this way, and since one of the symptoms of leptospirosis is meningitis, the original thesis contained some element of truth.

In every species it is the animals with the highest intelligence that most often show neurosis, and this fact would seem to fit in with Pavlov's experiments in showing that neurosis occurs when the intelligence of the animal is strained.

Treatment and future research.—As in-breeding appears to be one of the main factors causing neurosis in animals, it should be possible to produce animals with stable temperaments by cross-breeding, or, if necessary for other reasons, at least only line-breeding. Since temperament is inherited, any animal known to be neurotic should not be allowed to breed. In practice this policy can never be followed strictly, because if the animal is, for example, a high milk yielder, the farmer will wish to breed from her regardless of her temperament.

The problem, then, becomes one of cure rather than of prevention; much can be done by the human beings in contact with the animal, but it is doubtful if this ever constitutes a permanent cure: the neurosis will not be apparent while the animal is with that particular person, but the unstable temperament remains, and if the environment changes for the worse, the neurosis will reappear.

Finally, it is interesting to speculate on the possible future developments of research in animal behaviour. There are many strange stories connected with animals; one which is a first-hand experience of the author is of a saloon car in which a dog had suddenly become hysterical; the windows of the car were shut and nothing unusual could be heard from outside. The car passed by a pack of hounds waiting at a meet, and within a few seconds more than half the hounds were having an attack of hysteria. There are numerous accounts of animals being conscious of events occurring hundreds of miles away; no doubt some of these can be put down to coincidence, or imagination, but they cannot all be explained, any more than the homing instinct of animals can be explained.

It seems that we must acknowledge that animals have sensory receptors that we do not understand, and cannot, as yet, locate, and it may well be that these receptors receive the trigger stimuli responsible for hysteria in dogs, and in other animals. Professor Rhine, in America, and Dr. Thouless, in this country, have done pioneer work on extra-sensory perception (E.S.P.), and we can no longer deny that E.S.P. does exist in man ; perhaps we can learn more about it from studying the behaviour of animals.

Summary.

The forms which neurosis takes in various farm animals are described, and the relative importance of heredity, environment and diet as contributory causes is discussed. Possible methods of treatment are considered.

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ALIENS' PARANOID REACTION.

By F. F. Kino, M.D..

Middlewood Hospital, Sheffield, 6.

Psychotic states due mainly, but not exclusively, to unusual external circumstances are well known, and are commonly exemplified by such mental disorders as are occasionally met with in persons in prison, or those morbidly homesick, or suffering under the strain and stress of advanced deafness. In the great majority of these instances, however, the external conditions represent only an additional, precipitating aetiological factor which is operating as a trigger mechanism to a mental derangement of non-specific character already present in a latent state. It may therefore be of some theoretical and practical interest to report on a group of acute and subacute psychotic states whose history, features, course and outcome characterize them as constituting a readily recognizable clinical entity of purely psychological, situational origin.

During the years 1948 49 a number of young men of Polish nationality were admitted to this hospital under certificate or as voluntary patients. All of them arrived in this country after the war. Their ignorance or very defective knowledge of English was a great handicap to a deeper analysis of their mental states, though my own knowledge of the Polish language was sufficient to allow me to get in good touch with them, make them converse in their native tongue and peruse their writings. In most of these cases the clinical aspect and progress was so similar and at such variance with the common features of an affective or schizophrenic disorder that the particular character of the psychotic state very soon became evident.

Short extracts from the case-histories may illustrate the particularity of this mental aberration.

T. N—, 28 years, single, admitted 27.ii.49 as a voluntary patient in an acute state of agitation and panic, hallucinated vividly, heard people saying that he was to be killed and thought the police were following him. He knew where he was and tried to co-operate and to answer to simple questions. When reassured he asked in a frightened and subdued voice: "Have I really got to die?" After a fairly good night (with sedatives) he was able to give a fair account of himself. He had been at secondary school when the war broke out in 1939, entered the Polish Army at the age of 18, remained with the Forces for seven years, sharing first the strains of the war, the miseries of imprisonment in Russia, the wanderings of the Polish A.C., the fighting in Italy, until 1946, when he came to this country. He had never been seriously ill before, though very sensitive and homesick for his old mother in Poland. No mental disorders in his family. He was otherwise in fair health and of good physique. He became gradually quieter, and able to discuss the circumstances which led to his nervous breakdown. After discharge from the Army he had done heavy manual work, digging lime, which did not satisfy him, being so inadequate to his standard of education. He lived fairly solitarily, and the exhausting work left little time and energy to learn English. For the past few months he had had an affair with an older and married English woman and he now felt that this was wrong. He had grown restless and suspicious, believed that everyone knew about it, heard his fellow workers talking about him though he could not understand their English, was sure he would be killed and there was no

more hope for him. He assured me again and again of his innocence as to any other accusations. Gradually he became quieter, but four weeks after admission had an acute relapse with anguish, hallucinations and delusions. E.C.T. was without effect, but good recovery followed a course of insulin comas. He was discharged on 6.viii.49 in good mental state, grateful, cheerful, sociable, and fit to go back to his work.

St. G—, 25 years, single, admitted 24.ix.48 under certificate. On admission he was highly agitated, emotional, and in a state of anguish. For the next few days he remained restless, resentful and unable to give a sensible account of himself, complaining that his memory for the events of the past few weeks seemed unreal and confused. He was of good physique, and as he assured, always in good physical and mental health. No mental illness in his family. He came to this country in 1946 with the Polish A.C., and after discharge from the Forces worked as a cook in a miners' hostel among his compatriots. His knowledge of English was almost *nil*. About three months prior to admission he started to feel lonely and homesick, became restless and suspicious, believed that people thought him a spy, experienced strange illusions of smell and taste, the cigarettes tasted badly and he smelled an odour of corpses. He destroyed a wireless set because he thought it was specially prepared to spy on him. He found a lot of indirect remarks about himself in the newspapers, although he could not read English. After a fair improvement he suddenly relapsed with agitation and a suicidal attempt. Eventually he made a fair recovery, though still a little mistrustful and solitary. He was of average intelligence.

S. F—, 25 years, single, admitted 24.ix.49 as a voluntary patient. On admission he was difficult to approach, tense, suspicious, frightened, surly and hostile, but after a few days more approachable though still very reserved. He came to this country in 1946 with the Polish A.C. from Italy, where he had seen much hard fighting. He had always been physically and mentally well, and had worked lately as a general labourer. A few days before admission he complained of severe headaches, became frightened and excited, insisted on keeping the door closed, heard clocks ticking though no clocks were near. He disappeared suddenly from his hostel, wandered aimlessly about all night, came back the next day and reported to the police. When taken by ambulance to the hospital he suddenly jumped from the moving car looking suspiciously at everyone. When more settled he said that he could not remember correctly what had happened to him during the last few days. He thought that his friends had been avoiding him lately and talking about him in an unfriendly manner. Gradually he had become frightened. After several weeks in hospital he was more settled, though on occasions still depressed, and refusing food. He was of fair intelligence, though his knowledge of the English language was very poor. After a stay of seven weeks he left in a fair mental state, quiet, co-operative and sociable.

St. H—, 33 years, single, admitted 21.ii.49 as a voluntary patient complaining of severe headaches. He was wary and suspicious, but able to give a fair account of himself. He had served with the Polish forces, came to this country in 1947, worked in a pit and lived in a miners' hostel. The morning after admission he was in an acutely excited state, trembling, talking rapidly and relating spontaneously an extraordinary experience of the night before. He had seen the Holy Virgin standing at his bedside telling him that he was sent here to be destroyed but She would protect him. A friend of his who visited him reported that three months before he had told him that he would be poisoned because of a Polish girl. Later he became very restless, anxious and frightened. In hospital he remained for a while solitary, suspicious and moody but gradually became quieter, with better insight into being ill, though still inclined to exaggerate his well-being in order to get approval to leave. He said that he has noticed that during his stay here—and this seems to have a special meaning for him—his eyes have changed their colour. He states he has always been in good health, and nobody in his family has been mentally ill. He was of fair intelligence, but his English was very poor. Five weeks after admission he desired to be discharged and went back to his hostel.

W. W—, 37 years, single, admitted 16.v.49 as a voluntary patient after making an attack on another man with a bread knife in a quarrel. He was ignorant of English, quiet, rather dull, suspicious and reserved. He denied any mental trouble before. He was of farmers' stock and of very good physique. He served in the Polish army, was taken prisoner, spent five years in Germany working as an agri-

cultural labourer, came to this country in 1948 and worked in a steel works. He believed that the other inmates of the hostel he was living in persecuted him, called him a German and tried to steal his girl friend from him. He denied any hallucinatory experiences, but remained suspicious till his discharge after a stay of six months.

All these cases have several significant features in common which set them distinctly apart from other psychotic disorders with paranoid tendencies, namely, the premorbid history, the specific environmental circumstances at the onset of the illness, the characteristic clinical manifestations and the final issue of the psychotic episode.

A dependable account regarding the state of mental health in their families was not possible to obtain, though all of them denied any instances of mental ill-health among their relatives. Their personal state of health, at least for the past 6–8 years, could be more readily ascertained by the known and partly documented histories of that period in their lives. Though each of them was exposed for many years to the extraordinary physical and mental stresses of war, captivity, exhausting wanderings with the Polish A.C., or German labour camps, none of them had a nervous breakdown or was seriously incapacitated in his efficiency for service or labour. It will be agreed that no harder tests could be invented in order to prove a good physical and mental health and a high grade of constitutional make-up in a man.

With transfer to this country all the dangers and strains of war or captivity were completely removed, and they could enjoy freedom and material well-being they had not known for years. One would expect that such a wholesome turn in their circumstances would rather have enhanced the good state of their mental health, and made them resistive to the minor troubles commonly associated with a transfer to foreign surroundings, especially since they had already been away from their own country for many years. However, as a matter of fact, as long as they continued to live within their own units or groups they felt well and relatively contented. The change occurred with their transfer to workshops or pits, where they found themselves isolated in a foreign environment whose language and habits were unknown to them, making every attempt at interpersonal approach very difficult. Being accustomed natively to a lively and voluble companionship, the impossibility of making conversation and friendly contact with their new companions left them emotionally upset. Misunderstandings and miscomprehensions unavoidable in such a situation evoked their suspicion and mistrust. Harmless talks or remarks of their fellow workers to one another were interpreted as hostile observations, though they were unable to understand the language. Gradually this morbid state of mind grew to such intensity that a rational appreciation of the environment became quite impossible.

In one or other instance the development of the psychotic state was nurtured or accelerated by some factual misconduct on their own part, which under normal conditions would hardly have led to self-reproach or fear of such intensity, but here it was utilized to rationalize the presumed hostile deportment of their surroundings. Others ascribed this presumed hostility to their nationality, their conduct during the war or to false accusations as to their political

opinions. The progressive emotional tension culminated in several instances in a state of elemental panic and confusion, with impulsive running away or suicidal preocupations. Some of them experienced vivid visual or auditory hallucinations whose content was closely connected with their delusional preocupations, corroborating their ideas of reference or persecution. Though unreasonable, their delusions were never bizarre or of a nonsensical character.

The predominant clinical features on admission were a state of agitation and fear, combined occasionally with slight confusion, deep mistrust and, rarely, emotional outbursts. Their expression and behaviour were adequate to their affective state and genuine, without a shade of theatricality. It was rather the natural deep grief of an innocent person suffering under false accusations and slander. After a few days' rest (and sedatives) a fair contact could be achieved, though they did not believe in reassurance, and insisted on the reality of their fears, delusions and illusions. Hallucinatory experiences, either frankly admitted or noticed by their behaviour, were rare. In milder cases they believed their food was being poisoned and refused it. Gradually the more intelligent of them felt the desire to talk of themselves, to assert their innocence again and again, to refer to their good conduct in Services and to testimonials of their superiors. Though they exaggerated the importance of some minor misbehaviour, false self-accusations were never expressed. Over-estimations of their personalities, either in the form of importance or martyrdom, were not observed. In states of anguish their consciousness was slightly clouded but was never lost, and they were never stuporose. In quieter mood they were fairly orientated, and able to give an accurate account of their remote history and partly of more recent experiences prior to the acute breakdown. They never had the feeling of being really ill or influenced by other people. From their conversation, letters to friends or relatives, sociable conduct and fair adaptability to hospital life it was evident that their intelligence was not impaired, though never above average.

Under non-specific psychotherapy, supported by E.C.T. and in one case by insulin coma treatment, they became gradually more settled, with more and more insight in the abnormality of their feelings and ideas, and were eventually able to go back to their former surroundings and occupations.

Discussion.

The external conditions which give origin to such psychologically determined mental reaction are fortunately rare, and therefore the number of publications dealing with this type of psychotic disorder is limited.

The three cases reported by R. Allers (1920) seem to be the first to refer to psychogenic mental aberration of similar kind. All of them foreigners in good mental health were admitted to a general hospital in Austria among German-speaking patients whom they could not understand, and with nobody to translate their own tongue. They soon developed an acute psychotic state conspicuous by fear, agitation, ideas of reference and persecution, with illusional distortions of harmless experiences and with suicidal tendencies. Allers, by calling these disorders "persecutory delusions of lingually isolated persons," emphasized the aetiological importance of language. The observations of Kurt

Schneider (1930) under the heading "Primary Delusions of Reference" are of kindred character, though he believes that the bewildering experience of being suddenly transplanted into foreign environment is of no less importance than the lingual difficulties. Similarly to the cases of Allers, the paranoid affect-storm developed acutely and resolved completely after several days, with full insight into the morbidity of their suspicions and fears. A case by F. Knigge (1935) belongs apparently to the same type as those described by K. Schneider. A young and healthy Hungarian girl, travelling by herself to Brazil, was suddenly overtaken in Hamburg by an acute paranoid excitement state, which cleared completely within ten days.

According to these authors their cases represented immature and emotionally unstable individuals, though of average intelligence. In a sudden and unusual situation in alien surroundings, combined with a physical and mental strain and aggravated by lingual embarrassment, they responded with an acute paranoid excitement state of short duration. The episodic character of the mental derangement is in the view of the authors of particular diagnostic significance, differentiating these "paranoid reactive states" from true "paranoid processes" characterized by insidious development and chronic progression. However, Schneider, though all his cases were of the acute type, presumed that such reactions may also occur without such stormy development. Some of our cases may serve as an illustration to this theoretically foreseen possibility. The acuity of the disorder, though of diagnostic value if present, is evidently not necessarily an obligatory condition. Of much more significance than the time factor is the psychopathological structure of the psychotic state and its obvious features as a genuine psychogenic reaction. In Jaspers' definition a "genuine reaction" is one in which "the thought content is in a comprehensible connection with the primary causal experience and which could not occur without that experience, being in its further progress dependent on that experience and its connections." Although morbid in the exaggerations and conclusions, it remains well comprehensible in its origin as rooted in a personal experience and an almost specific situation, and in the consequences of its further development.

It is probably true that some degree of hypersensitivity or deficiency in self-reliance, or both, will often be in the make-up of persons prone to respond with a paranoid reaction under adequate pathogenic conditions. However, as evidenced in our instances, even a quite healthy and emotionally well-balanced individual, when subjected to unusual affective stress in a specifically difficult situation, may respond in the same morbid manner. In the usual interplay between constitutional susceptibility and a selective situation, the determining causal agent in these cases is rather the character of the situation than the make-up of the personality.

It is hard to say what is the primary disturbance, whether it is one of affect or of misconception regarding the attitude of the environment, since both are often closely intertwined from the start. Loneliness, external difficulties and social maladjustment will quite naturally bring on a depressive mood, which in turn will falsify perceptions and judgment. The difficulty of language was no doubt a moment of great importance, but was not the exclusive one. The

sudden loss of their habitual companionship, the foreign surroundings with their incomprehensible atmosphere and habits, the change of occupation, the hazards of being on their own responsibility instead of being directed and cared for as before, all these various influences together were for many of them a too great emotional stress which, finding no relief by verbal expression or sympathetic consolation, broke through as a paranoid psychotic reaction.

In support of the correctness of the given interpretation it can be stated that after 1949 such mental disorders were no longer observed among Poles admitted to this hospital with psychotic disorders. After the first years passed the difficulties of language were naturally overcome, and little by little they learned to understand their new community better and to adjust themselves satisfactorily to their new life.

Conclusions.

A rare form of an acute and subacute psychotic disorder was observed during the years 1948–49 among Polish workers admitted to this country after the war.

On the strength of its aetiology, features, clinical course and issue the mental disorder is regarded as a genuine psychogenic psychotic reaction.

The suggested designation will express its particular origin and character.

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Part II.—Reviews.

Oedipus, Myth and Complex. By P. MULLAHY. London: Allen & Unwin, 1948. Pp. xix + 538. Price 37*s.* 6*d.*

The theories of psycho-analysis and its derivatives are described in this book with notes and bibliography, and Jebb's translations of the Oedipus Rex, Oedipus at Colonus, and Antigone are included.

The first four chapters are devoted to Freudian theory. In the second and fourth of these respectively its later modifications and applications to mythology are particularly well done. An extract from Plato shows how near he was to the modern theory of dream formation. The later chapters are of less significance to most British psychiatrists. They are given to the work of Adler, whose theories are too superficial ever to have attracted the latter, though, requiring little emotional effort for their understanding, they have fascinated the general physicians and public, and to Jung with his interesting and deliberate flight from reason to magic. Rank's conjectures that all happiness ends with the birth trauma and that truth is subjective are described, for he has a following in the U.S.A. Karen Horney's view that neurosis is a character disturbance is shown to have much to recommend it, but she is too preoccupied with typology. This also mars Fromm's theories which are intermediate between Freud's and Adler's. Sullivan's theories that satisfactions are related to muscular tensions seem incomplete and his ideas on child development seem limited to the American scene. A concluding chapter critically evaluates all these views.

Their relationship to the Oedipus is not everywhere apparent; nevertheless on cultural grounds it was a happy thought to include Sophocles's trilogy in this volume. The introduction, by Fromm, contains this amazing sentence on p. iv: "We know much about the atom, we know less about the living cell, and we know even a great deal less about the mind." In the body of the book the writing, though generally adequate, is spoiled by the current vulgarisms of "due" when "owing" is meant on pp. 54, 64, 68, 252, and "so as" instead of "in order" on p. 254. The book is expensive.

E. S. STERN.

Frustration. The Study of Behaviour without a Goal. By NORMAN R. F. MAIER. London: McGraw-Hill, 1949. Pp. xiii + 264. Price 21*s.*

The first part of this book describes experiments by the author, using the Lashley jumping apparatus, in which rats were given the choice of two alternatives, one being rewarded and the other punished. By jumbling these consequences the problem was made insoluble. Thus the animal was frustrated. In such cases Prof. Maier commonly found that the response became fixated, the experimental rat invariably making one particular choice regardless of the consequences, even if the situation had long been altered so that these were constant and predictable. This property of fixation could only be altered by "guidance," otherwise it seemed to persist indefinitely. Severe punishment aggravated it, but reward may occasionally cause some relief. These results are clearly of great importance if universally valid, but recent experiments in England have not been quite so definite.

Nevertheless the work is of great interest. The author suggests that its

application to man would indicate that recidivism and compulsive behaviour result from frustration and this explains their intractability to punishment and recognised treatment respectively. He enlarges the matter further but does not point out that it is incompatible with the doctrine of freewill, a philosophical consequence of some importance. It is particularly in the latter part of the book that he develops the implications and applications of his theory. He suggests that there may be conflict between goal-motivated and frustration-instigated behaviour as well as between two choice situations. He applies his theory well to child management, though it must be admitted that nothing startling emerges in the final result.

These researches are refreshing in their interest and originality, and even if they should be disproved Prof. Maier has given us a novel and stimulating view of our daily problems.

E. S. Stern.

Cell Growth and Cell Function. By Professor Torbjoern O. Caspersson. New York: W. W. Norton & Co., Inc. London: Chapman & Hall. Pp. 185. Figs. 91. 28*s*.

For twenty years the author and his school have studied the biochemistry of the intact cell, using chiefly the methods of ultraviolet spectrography applied to the microscopic image. By using a variety of wavelengths for the photomicrography, and by comparing the observed absorptions with those of known substances, he has been able to deduce with some confidence the chemical nature of many important cellular constituents. A picture can thus be built up showing not only the global quantities but also the naturally occurring gradients of concentration. In his Salmon Lectures the author summarized his work, and this book presents his results in expanded form.

It can certainly be recommended. Profusely illustrated and well bound, it contains much information that will interest the biochemist and histologist. The psychiatrist, too, will be interested, for Caspersson studied the nerve cell and found, rather to his surprise, that it is remarkably active in protein synthesis, being at times inferior in activity only to the developing ovum. Why this should be is still unknown, though there is evidence that the synthesis plays an important part in normal neuronic function. It was the idea that this synthesis might be faulty in schizophrenia that first led his colleagues Hydén and Hartelius to treat this condition with malononitrile.

W. Ross Ashby.

Pavlov: A Biography. By B. P. Babkin. London: Victor Gollancz, Ltd., 1951. Pp. 365. 25*s*.

Professor Babkin, who died just before the book was published, was a pupil of Pavlov's at the Institute of Experimental Medicine and worked with him for over ten years. The two became close friends and remained so throughout their lives, though they had to separate eventually when Babkin went to Canada. Here Babkin wrote the book, and though the location made some Russian material and information unavailable, it left the author free from any suggestion of political pressure. As a Russian, a lifelong friend, and a professional physiologist, the author was obviously well qualified for the task.

The resulting book is excellent. It is written in good English and is rich in facts. It reveals Pavlov's genius, yet is by no means blindly hero-worshipping. All those who have been thrilled by Pavlov's discoveries will want to know something of the man himself: Babkin's book will give the information they want.

W. Ross Ashby.

Mental Health Through Will Training. By ABRAHAM A. LOW, M.D. Boston: Christopher Publishing House, 1950. Pp. 393.

The material of this book consists of descriptions of a form of group therapy used by the author, with quotations from his patients' utterances and the explanation he gives in return. While the very circumstances of these pronouncements may well excuse a certain inaccuracy and popular form of expression, the reader would still expect to find, somewhere in the book, some clear statement of the writer's standpoint and beliefs. His standpoint is, at least negatively, expressed by him in his preface, when he says, "I cannot share the view that human conduct is the result of unconscious drives, sexual or otherwise." The system of help given to the patients under the auspices of Recovery, Inc. (of which Dr. Low is the Director), seems a mixture of self-help *à la* Dubois, plus a good deal of suggestion based on the popular conception of the will as the only agency for ordering our lives and controlling our impulses and even our beliefs.

The author's style, however, is so racy, journalistic and propagandist that psychological precision is sacrificed for the sake of quick appeal, and nowhere does a clear view of the author's psychological beliefs emerge. What are we to make, for instance, of the author's use of the terms "relaxed feelings" or of his attempted distinction between feeling and temper, or of his definition of temperament as the "sum total of original responses of which a person is capable"?

Enough has been said to warn readers that here will they find no reasoned account of either theory or technique, but only a kind of exhortation that might be of some limited value in a popular journal of the "How-to-Control-your-Mind" type, but should never be the basis of a serious book on psychotherapy.

J. ERNEST NICOLE.

Adler's Place in Psychology. By LEWIS WAY. London: George Allen & Unwin, 1950. Pp. 317.

It is not always easy, from Adler's own voluminous writings, to obtain a clear conception of his system of psychology, and Mr. Way has rendered a real service by categorizing so clearly the views of the Adlerian School. This he has done efficiently, soberly, and with much more regard for the exponents of other schools than is usually found in books of this kind.

Particularly useful are his discussions of the relationship between Adler's viewpoint and psychoanalysis, Behaviourism, McDougall's School, Kretschmer and Jung. The author admits one criticism of Adler, namely that his views are biased by too strong a partiality towards the extraverted view of life. The final chapter on Adler's cultural background is specially interesting.

The book is clear, sound, comprehensive, and is strongly recommended for all requiring a systematic statement of the Adlerian standpoint.

J. ERNEST NICOLE.

What is Hypnosis? By ANDREW SALTER. London: The Athenaeum Press, 1950. Pp. 95.

This little book is of importance, because it aims at giving an explanation of hypnosis in the light of conditioned responses. It leans heavily on Kretchmer's views concerning the release of such primitive functions as hyponoic thought and hypobulic behaviour, and it stresses by means of most interesting case-histories the therapeutic use of autohypnosis. The author does not profess to have answered all possible questions, and indeed indicates directions in which further research is urgently needed.

The book can be recommended as a genuine attempt to place hypnosis on a sound basis, thereby lifting it from the mumbo-jumbo with which it tended at one time to be associated.

J. ERNEST NICOLE.

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Some Biochemical Changes Observed during Agene(R)-Induced Convulsions.

It is shown that there are biochemical changes in the blood of dogs exhibiting canine " epilepsy " induced by agene(R)-treated proteins that are similar to those reported to occur in human epilepsy.

The observed changes, which are described in detail, are briefly as follows :—

1. Glucose :

(*a*) A significant decrease in venous glucose prior to the first convulsive attack.

(*b*) A significant rise in both arterial and venous glucose during the convulsion. The arterial glucose is lower than normal in the interparoxysmal stage.

2. Serum potassium and magnesium : A rise in the interparoxysmal stage.

3. Carbon dioxide : A decrease in both the arterial and the venous blood during the convulsive attack, with persisting levels below normal in the venous blood in the interparoxysmal period.

4. Calcium oxygen and cholinesterase : No changes at any stage.

5. Serum inorganic phosphorus : Whereas the serum inorganic phosphorus was not found to change significantly, there was a suggestive rise at the time of the convulsive attack. (Authors' abstr.)

Temperature Regulation in Schizophrenia : 1. Comparison of Schizophrenic and Normal Subjects. 2. Analysis by Duration of Psychosis.

This investigation has been concerned with homeostatic function of the autonomic nervous system in schizophrenia. Temperature regulation was selected for study as a suitable example of homeostatic activity.

The investigation was divided into two parts. In the first a comparative study of the diurnal temperature cycle and the temperature response to heat and cold was made in a group of normal subjects, and in a series of 40 schizophrenic patients prior to the operation of lobotomy.

In the second part, the status of temperature regulation according to the duration of the psychosis was analyzed. For the analysis of the diurnal temperature cycle, a larger series of patients was studied, in order to include patients at the two extremes of the duration range.

The findings in this investigation have indicated that homeostatic autonomic function, if adequately represented by temperature regulation, is disturbed in schizophrenia, particularly during that period in which the psychosis, although definitely established, is relatively early and acute.

The interpretation of these results is discussed, the apparent relation between the course of the psychic and that of the physiological characteristics of the disease being stressed. (Authors' abstr.)

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Poliomyelitis : IV. A Study of the Midbrain.

1. The midbrain, although frequently involved in bulbar poliomyelitis, is never as severely implicated as the lower region of the brain stem.

2. Within the midbrain the severest involvement is generally observed within the oculomotor nuclei, the substantia nigra and the tegmental nuclei.

3. There are three sets of tegmental nuclei within the midbrain—the lateral, the ventral and the dorsal tegmental nuclei. Structurally these cells do not resemble the reticular cells of the medulla, but seem to be much more similar to the cells of the substantia nigra, to which they appear related.

4. Clinically, little evidence can be observed in patients with bulbar poliomyelitis to indicate extensive involvement of the tegmental nuclei.

5. In spite of the frequent and extensive involvement of the substantia nigra, little evidence of implication of the extrapyramidal system can be detected in cases of bulbar poliomyelitis. This is assumed to be due to the acuteness of the illness and the rapid fatality in these cases.

6. The oculomotor nuclei of the midbrain are only moderately implicated in bulbar poliomyelitis, and their involvement appears to correlate fairly well with ocular symptoms. (Authors' abstr.)

Lobotomy and Psychopathology.

The authors have demonstrated how the Malamud-Sands clinical psychiatric rating scale may be used in evaluation of the effects of lobotomy on the psychopathology of a group of 31 psychotic patients. Their analysis revealed that certain behavior patterns were favorably, and others were adversely, affected. Certain phenomena regarded by some investigators as unalterable were found to be influenced by this treatment. (Authors' abstr.)

Value of Convulsive Therapy in Juvenile Schizophrenia.

On the basis of the present study, the conclusion seems justifiable that the convulsion therapies do not appear to influence the course of schizophrenia when occurring in patients before the age of 18 years. Juvenile schizophrenia tends to run a malignant course. (Authors' abstr.)

Pneumoencephalographic Changes following Prefrontal Leukotomy (Freeman-Watts Technic).

Nineteen unselected cases in a series of 32 consecutive leukotomies were studied by pneumoencephalograms shortly before and up to 20 months after operation. The leukotomies were performed in accordance with the Freeman-Watts technic on patients with refractory psychoses of varying age groups.

The pneumoencephalographic changes in these 19 cases have been described in considerable detail. In nine of these the pre-operative pneumoencephalograms were normal in all respects. In five of these nine cases post-operative studies showed diffuse dilatation of the ventricles, and in all of the nine there was a significant absence of air in the subarachnoid space surrounding the brain. In one case there developed a large porencephalic cyst, occupying almost all of one frontal lobe.

In five cases the ventricles appeared normal pre-operatively, but there was an increase in the sulcal markings. Post-operatively the ventricles also showed progressive dilatation with obliteration of the subarachnoid space surrounding the brain. In one of these five a porencephalic cyst also developed. In the remaining five cases studies pre-operatively there was diffuse or localized ventricular dilatation. In four of these there developed frontal porencephalic cysts, progressive ventricular dilatation and obliteration of the subarachnoid space surrounding the brain.

The related pathologic changes found in five of seven cases in which autopsy was performed were as follows: (*a*) cystic necrosis of the frontal lobes, (*b*) atrophy and gliosis throughout the brain, (*c*) meningeal thickening, scarring and hemorrhages, (*d*) generalized enlargement of the ventricles, most prominent in the frontal horns, and (*e*) cystic degeneration of the thalamus and basal ganglia, particularly in the nucleus medialis dorsalis of the thalamus.

The hydrocephalus described as a roentgenographic finding is probably due to a combination of cerebral gliosis and atrophy and a decrease in the absorptive function of the arachnoidal granulations. It may also be related to some extent to obstruction to the free egress of spinal fluid between the basal cisterns and the subarachnoid space overlying the brain.

Porencephalic cysts occurred with greater frequency in those cases in which dilatation of the anterior horns of the lateral ventricles was present pre-operatively, either as a localized dilatation or as a part of generalized enlargement of the ventricular system. The authors feel that this incidence is easily explained by the fact that the anterior horns of the dilated ventricles are more easily penetrated by the leukotome at operation.

These findings are consistent with those in the cases reported in the literature.

To prevent this occurrence, the authors suggest that pneumoencephalographic studies be included in the pre-operative work-up in all cases of prefrontal leukotomy. In those cases which show dilatation of the frontal horn of the ventricle, the surgical technic should be modified accordingly. (Authors' abstr.)

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Effects of Decamethonium Bromide (C10) *and* d-*Tubocurarine on Electroconvulsions.*

The "curarizing" effects of *d*-tubocurarine chloride and decamethonium bromide (C10; decamethylene-1, 10-bistrimethylammonium dibromide) were compared in a group of 50 patients undergoing electric convulsion therapy for various psychiatric disorders.

The "curarization" effects of the two drugs were essentially similar in 66 per cent. of the patients. In 20 per cent. adequate relaxation could be produced with decamethonium bromide, whereas respiratory distress without optimal "curarization" was produced with *d*-tubocurarine chloride. In 14 per cent. optimal relaxation without respiratory distress could not be obtained with either drug. In no case did *d*-tubocurarine chloride produce optimal "curarization" without the same effect being achieved with decamethonium bromide.

There was no significant correlation between tolerance to one drug and that to the other, or between adequacy of response or degree of tolerance to either drug and the age and weight of the patient.

No complications, such as compression fractures or dislocations, were encountered in any patient even when the dose of the drug was insufficient to produce complete relaxation.

Decamethonium bromide is an improvement over *d*-tubocurarine chloride in modifying electric convulsion therapy in that histamine-like reactions are absent, the duration of paralysis is shorter and respiratory distress with intensely "relaxing" doses is less frequent. (Authors' abstr.)

Effect of Prefrontal Lobotomy on Temperature Regulation in Schizophrenic Patients.

In this report post-lobotomy changes in temperature regulation are described for a group of 40 schizophrenic patients. These changes brought the patients closer to the normal through a lessening of irregularity and rigidity in the pattern of temperature regulation. The post-operative change was greater in those

subjects who differed most from the normal before operation, namely, in the group with relatively early psychoses.

In the interpretation of these findings, it is suggested that the pre-operative abnormalities result from the disturbing influence of the prefrontal cortex on lower autonomic centers. This disturbance would appear to diminish naturally as the psychosis approaches chronicity, and to be removed artificially by lobotomy.

(Authors' abstr.)

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The Origin, Course and Termination of the Prefronto-Pontine Tract in the Human Brain.

(1) Six cases have been presented showing circumscribed, essentially prefrontal lesions, a fact confirmed by cytoarchitectonic examination. They have been compared with 22 further cases, in many of which the lesion includes anterior portions of area 6/FB.

(2) The existence of a prefronto-pontine bundle arising from granular prefrontal cortex has been established in three hemispheres, in which the primary lesion terminates at a level anterior even to the dysgranular area 8/FC, and where the entire frontal lobe posterior to the leucotomy cut is free from any significant incidental lesion. In these three cases the degenerated tract can be traced through the internal capsule and the medial portion of the cerebral peduncle to its termination within the medial fascicles of the pons. The nerve cells surrounding these fascicles display transneuronal degeneration. All but one of the remaining 25 cases show degeneration of the prefronto-pontine and/or fronto-pontine tracts.

(3) The prefronto-pontine tract is shown to be derived from the dorsal as well as from the lateral convexity of the prefrontal region. The extreme pole and the entire orbital surface do not contribute.

(4) The question whether the cingular suppressor area contributes to the prefronto-pontine tract cannot be decided on the present material.

(5) A certain overlap of thicker fibres from dysgranular and agranular areas seems to exist in Arnold's bundle, which would therefore be better classified as a tract carrying simultaneously prefronto-pontine, as well as fronto-pontine components. This is in agreement with experimental evidence in the literature.

(6) The size of the degenerated area within the cerebral peduncle varies in proportion to the extent of the lesion from a medial one-sixth in those cases with exclusively prefrontal involvement to a medial one-fifth in those with additional damage to anterior zones.

(7) No cortico-nigral fibres originate anterior to area 6/FB.

(8) It is suggested that individual variations may exist regarding the fibre composition of the fronto-pontine system. One case with complete absence of at least the anterior component of this system is described in detail. A bilateral occurrence of this and similar anomalies has been noted. (Author's abstr.)

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Frontal Lobe Functions and Intelligence.

Some conceptual and methodological difficulties which are retarding progress in understanding brain and behaviour in general and frontal lobe functions in particular are pointed out. These include difficulties in establishing a suitable unit of behaviour, in specifying the " lesion," in calibrating the behavioural scales, and in controlling learning effects in repeated measurements.

Attention is directed to Binet's distinction between intellectual level and intellectual activity. It is suggested that level is homologous with the cerebral power factor P, while activity is homologous with the abstraction activity factor A. These factors have been identified by the writer as components of biological intelligence.

The possibility remains to be explored that psychosurgery is effective by establishing a more " optimal " balance in the ratios between power factor P and abstraction activity A. (Author's abstr.)

Frontal Lobes and Emotion.

The frontal lobes are profoundly concerned with emotions by virtue of the cingulate gyrus-orbital cortex connections and the orbital cortex-temporal lobe connections. In general, the cingulate gyrus probably serves the function of recognition of instinctive drives and their effects which is tantamount to recognition of emotion. The orbital cortex is essential to introspection and wisdom. The frontal-temporal connections are essential to normal instinctive behaviour. A lesion in any of those locations profoundly disturbs instincts and emotions.

(Author's abstr.)

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Spontaneous Electrical Activity of the Spinal Cord.

1. The isolated spinal cord of frogs and cats shows spontaneous electrical activity which can be registered without difficulty. In the electrochordogram it is possible to distinguish slow and fast waves.

2. A single isolated segment of the frog's spinal cord also shows spontaneous electrical activity.

3. The spontaneous electrical activity is maintained at a relatively high level by stimuli which are transmitted from the skin and muscles of the spinal cord. After section of all the spinal nerves, peeling-off of the skin and elimination of proprioceptive stimuli by injection of curare, the spontaneous electrical activity diminishes considerably.

4. The spontaneous electrical activity of the spinal cord is also influenced by the brain. Both the nuclei of the brain stem and the motor cortex of the cerebral hemispheres play an important part in this respect. (Author's abstr.)

The Stability of a Random Assembled Nerve-network.

As part of a program for studying cerebral dynamics, an analysis has been made of the general problem of how a system will behave if it is formed by the random assembly of many parts. In particular it was hoped that the investigation would throw light on the significance of the oscillations seen in the electro-encephalogram.

Several methods were used. The homeostat was used extensively to explore

the possibilities, and the mathematical methods were used to extend the range. These methods are considered to provide the appropriate symbolism for the study of " open " physical systems.

The facts have led to the following conclusions :

(1) The stability of the whole is not deducible from the stabilities of the parts. Examples are given showing that parts all unstable may form a stable whole, and the converse.

(2) If a single part becomes intrinsically very stable it tends to become constant and to lose its effect on the behaviour of the whole.

(3) If all the parts become very stable intrinsically, the whole becomes equivalent to a collection of isolated parts.

(4) Increasing the richness of connections between parts usually decreases the chance of stability.

(5) Stability and instability are not possibilities of equal likelihood ; there is a bias towards instability. In many typical cases the chance that a random assembly of n parts will be stable falls off as $(\frac{1}{2})^n$.

(Author's abstr.)

Behavioural and E.E.G. Changes following Chronic Brain Stem Lesions in the Cat.

The effect upon behaviour and the E.E.G. of chronic lesions in the rostral brain stem has been studied in a series of cats.

Of lesions in sensory paths in the periaqueductal grey, or in the midbrain tegmentum and basal diencephalon, only the latter, in a position to interrupt the ascending reticular activating system, were followed by chronic somnolence and E.E.G. synchrony.

Activation of the synchronized E.E.G. by somatic and auditory stimulation was still possible either after the reticular activating system or after long sensory paths had been interrupted immediately behind the thalamus. Collateral sensory excitation of the reticular activating system in the lower brain stem, and the direct arrival of afferent impulses at some site above the midbrain, thus serve equally well to induce E.E.G. arousal, but only in the former instance does prolonged wakefulness follow.

Poverty of behaviour after lesions of the reticular activating system suggests that its influences may be directed both cephalically to activate the E.E.G. and caudally to facilitate motor activity, in maintaining the waking state.

(Authors' abstr.)

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Reitman's Pin-Man Test. A Means of Disclosing Impaired Conceptual Thinking.

(1) Reitman's Pin-Man Test is described and the method of scoring it discussed in detail. It is taken to measure simultaneously the subject's capacity for abstract thinking, for empathy and for perceptually organizing material shown to him.

(2) It is demonstrated statistically that the test effectively distinguishes between deteriorated and non-deteriorated subjects, and gives consistent results when repeated with the latter.

(3) The test appears a satisfactory means, therefore, of registering changes in conceptual thinking, concreteness of outlook, emotional understanding, etc., either under the influence of a disease process, or following treatment, such as a prefrontal leucotomy. (Authors' abstr.)

The Anti-convulsive Action of Histamine and of Other Vasodilating Drugs on Experimental Convulsions in Man.

The anti-convulsant action of histamine and of other vasodilating drugs on metrazol and electric convulsions has been examined in 42 patients on 170 occasions.

The results prove unquestionably that the anti-convulsive action of histamine is powerful for metrazol seizures. The anti-convulsive action of acetylcholine bromide was about 80 per cent. that of carbaminoylcholine (Doryl) to 37 per cent., that of amyl nitrite to 30 per cent., in comparison to that of histamine. Nicotinic acid and nitroglycerine were not capable of inhibiting convulsions at all.

The anti-convulsive action of histamine is in proportion to the amount of the drug used, and it lasts a very short time, 25 to 40 seconds, during the sharpest fall of blood pressure caused by the drug.

The anticonvulsive action of histamine is not inhibited by adrenalin and ergotamine tartrate.

On the basis of the author's experiments and some literary data the author states that the anti-convulsive action of certain vasodilator drugs examined by him are not induced by cerebral vascular changes caused by them, nor is the metrazol seizure. The anti-convulsive effect seems to result from a special action exerted on physico-chemical processes (permeability, polarization) of the nerve cell membrane directly. Histamine and acetylcholine are most capable of exerting such action.

The author has not succeeded in inhibiting electric seizures by histamine. For this reason it seems possible that the pre-convulsive mechanism of the metrazol seizure is of a different nature from that of the electric seizure.

(Author's abstr.)

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Memory Studies in Electric Convulsion Therapy.

Studies are described of the re-arousing of verbal responses by a series of pictures resembling, though not identical with, a series of pictures seen earlier. The subjects were 46 patients undergoing E.C.T. and 12 matched controls.

It was found that patients who were asked to give a verbal response to concrete pictures before a course of E.C.T. or during the early confusional period after it, gave the same verbal response more quickly than was expected to ambiguous pictures seen in the confusional state.

In well-orientated patients exactly the opposite effects were noted. If the patients were shown concrete pictures before the ambiguous ones, the ambiguous ones were responded to more slowly than if seen alone.

The relationship between these findings and some disturbances of memory noted in cases with known organic lesions is discussed, with references to further possible lines of research. (Author's abstr.)

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*Dendritic Potential of Cortical Neurones Produced by Direct Electrical Stimulation of the Cerebral Cortex. *Chang, H-T.* 1
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Dendritic Potential of Cortical Neurons Produced by Direct Electrical Stimulation of the Cerebral Cortex.

1. From the observation of Golgi and Golgi-Cox preparations the general arrangement of cortical neurons has been described with special reference to the distribution of the apical dendrites of pyramids in the molecular layer. On the basis of this anatomical fact the local cortical response to a single electric shock applied to the cortical surface has been analyzed.

2. The cortical response as recorded with a unipolar electrode from the points within about 5 mm. away from the point electrically stimulated consists of two components ; a sharp spike assignable to the dendritic potential, and a long-lasting slow wave representing the mass activity of the intracortical neurons.

3. The first component has a lower threshold and reaches its maximal magnitude sooner than the second component when the stimulus strength is gradually increased.

4. When the recording electrode penetrated into the cortex to a depth of about 1 mm. the polarity of the first component reversed while the second component remained, indicating that the first component is a process chiefly occurring in the superficial layer.

5. The interruption of the horizontal fibers by a shallow transverse incision between the stimulating and recording electrodes did not abolish the local cortical potential but reduced the amplitude, increased the latency and increased the initial positivity of the first component. An incision about 3 mm. deep, however, abolished the response completely.

6. The conduction velocity of nerve impulses propagating along the horizontal course of the apical dendrites as determined on the cortical surface is about 1 m. per second in cat, and 0·6–0·7 m. per second in monkey.

7. Differentiation and localization of the cortical dendritic potential were also made by the method of laminar blocking of the function of cortical neurons by superficial application of novocain on the cortex.

8. Anoxia produced by inhaling pure nitrogen abolished the second component earlier than the first, suggesting the occurrence of blockage at the axon-soma junction which prevented the passage of nerve impulses from the dendrites to the axon. (Author's abstr.)

An Observation on the Effect of Strychnine on Local Cortical Potentials.

The pattern of the local cortical potential could be modified by superficial application of strychnine on the cerebral cortex so that both the size and the promptness of onset of the second component were enhanced without significantly affecting the first component. When the action of strychnine was fully developed, the two components became fused into a single wave which, however, could be dissociated again into two temporally separated waves by reducing the stimulus strength. It is suggested that the effect of strychnine is probably to accelerate the process of impulse initiation of individual neurons in the central nervous system so as to increase the efficiency of summation, and to increase the chance of synchronization. (Author's abstr.)

Role of Acetylcholine in Nerve Activity.

By the use of DFP the minimum acetylcholine esterase activity required for maintaining pupillary function has been established. This result, considered as an isolated phenomenon, does not make possible a distinction whether synaptic transmission or axonal conduction is interrupted if the enzyme activity falls to a low level. However, the great variety of biophysical and biochemical facts accumulated during the last few years support the assumption of a similarity of the basic nature of the two processes. They have given a satisfactory explanation for the peculiarities observed at the synapse. There is no longer a basis to assume a special mechanism there as proposed in the original theories of chemical transmission. It thus appears justifiable to consider the minimum enzyme activity found as being part of the mechanism necessary to maintain synaptic transmission and axonal conduction.

The confirmation of the presence of choline acetylase in optic nerve fibers—in itself again not conclusive as evidence for the essentiality of acetylcholine in conduction—removes one of the main objections still maintained against Nachman-

sohn's theory. The presence of the enzyme becomes pertinent in connection with the observation that all types of nerves, including the optic, contain acetylcholinesterase and that inhibitors of this enzyme block conduction.

(Author's abstr.)

Effects of Combined Destruction of Frontal and Posterior "Associative Areas" in Monkeys.

Four monkeys (*Macaca mulatta*) with bilateral parieto-temporo-preoccipital ablations were subjected to subsequent removal of frontal granular cortex. Tests and observations of sensory status and of discriminative capacities in vision, somesthesia and audition were made before and after the frontal operation. More complex functions (conditional reaction and delayed response) were also tested. Protocols were kept on general behavior and levels of activity. The effects of the additional prefrontal ablation are summarized below:

1. A decrease in visual acuity was found in one monkey, and a constriction of the visual field in another. No other primary sensory defects were observed.

2. Deficits in retention or relearning of some of the somesthetic discrimination problems (roughness and temperature) were found in two of the subjects. No deficits were demonstrable in the visual discrimination problems or in a learned auditory association.

3. Additional decrement on the conditional reaction problem resulted from the subsequent prefrontal excision.

4. Three animals failed completely on the problems requiring delayed response, and the fourth showed marked decrease in ability.

5. General activity was greatly increased in all animals.

These data, with those from previous experiments, are discussed in relation to the mode of representation of function in associative cortex. (Authors' abstr.)

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1. Biochemistry, Physiology, Pathology, &c.

Histochemical Distribution of Cholinesterase and Acid Phosphatase in the Prefrontal Cortex of Psychotic and Non-psychotic Patients. Pope, A., Meath, J. A., jun., Caveness, W. F., Livingston, K. E., and Thomson, R. H. [*Trans. Am. Neurol. Assoc.*, **74**, 147–53 (1949).]

Biopsy specimens excised from Brodmann's area 9 of the prefrontal cortex during the initial stages of prefrontal lobotomy showed greater cholinesterase activity and lower acid phosphatase activity in schizophrenics than in non-psychotics undergoing lobotomy for intractable pain. Acid phosphatase activity was greatest in axones and in the cell bodies of the larger cortical ganglion cells.

MARION HORN PESKIN (Chem. Abstr.).

Effect of Acetylcholine on the Resistance of Guinea-pigs to Anoxemia. Franck, C., Grandpierre, R., and Didon, P. (*Faculté Méd., Nancy, France*). [*66th Congr. French Assoc. Progress Sci., Sect. Pharmacol.*, 1947; *Toulouse méd.*, **49**, 10–13 (1948).]

Experiments made with dogs and rabbits (Cluzet *et al.*, *Comp. rend. soc. biol.*, **121**, 695 (1936); *Bull. acad. méd.* (*Paris*), **120**, 241 (1938); *J. physiol. et path. gén.*, **36**, 50 (1938), were performed with guinea-pigs. Acetylcholine increased their resistance to lack of O and to low pressures. G. SAG (Chem. Abstr.).

Effects of Anesthetics and Convulsants on Acetylcholine Content of Brain. Elliott, K. A. C., Swank, Roy L., and Henderson, Nora. (*McGill Univ. Montreal, Can.*) [*Am. J. Physiol.*, **162**, 469–74 (1950).]

Following administration of nembutal the acetylcholine (ACh) in rat or cat brain rises to a high maximum. It falls as anesthesia wears off, but can be raised again by further administration of the drug. Other anesthetics also increase the ACh level. Following metrazole or picrotoxin administration, the ACh level is lowered in nembutalized cats, but somewhat raised in unnarcotized cats.

E. D. WALTER (Chem. Abstr.).

*Anemia due to Acetylcholine. Fornaroli, P., and Antona, G. (Univ. Pavia, Italy). [Boll. soc. ital. biol. sper., **25**, 1297–9 (1949).]*

Injection of acetylcholine hypodermically in rats and rabbits causes hyperchromic anemia with diminution of the red cells to 2·5 million per cu. mm. in the rat and 1·5 million in the rabbit. The degree of anemia is proportional to the dose. Treatments with antipernicious anemia liver extract or with folic acid induces a prompt remission of the anemia. Treatments with liver extracts deprived of the antipernicious anemia factor or with extracts of kidney or spleen are ineffective.

M. Elliott (Chem. Abstr.).

*Phenylpyruvic Oligophrenia. Mautner, Hans, and Quinn, Karl V. (Wrentham State School, Wrentham, Mass.). [Ann. Paediat., **172**, 1–27 (1949).]*

Large amounts of $NaHCO_3$ and vitamin C depressed excretion of phenylpyruvic acid. Tyrosine and glutamic acid effected no improvement.

Barbara R. Murray (Chem. Abstr.).

*Excretion of Phenylalanine and Derivatives in Phenylpyruvic Oligophrenia. Jervis, Geo. A. (New York State Dept. of Mental Hyg., Thiells). [Proc. Soc. Exptl. Biol. Med., **75**, 83–6 (1950).]*

Quantitative data are presented on the urinary excretion of phenylalanine (I), phenylpyruvic acid (II), and phenyllactic acid by 20 patients (ages 2–42 years) affected with phenylpyruvic oligophrenia. The values, expressed as mgm. per gm. of total N, show no important differences from patient to patient kept on similar diets. High protein diet or ingestion of (I) or (II) increases the output. Sweat from 10 of the subjects contained 1·4–9·6 mgm. per cent. of (I) and 6–56 mgm. per cent. of (II).

L. E. Gilson (Chem. Abstr.).

*Oligophrenia Phenylpyruvica. (II) Constancy of the Metabolic Error. Borek, Ernest, Brecher, Arthur, Jervis, Geo. A., and Waelsch, Heinrich. (Columbia Univ.). [Proc. Soc. Exptl. Biol. Med., **75**, 86–9 (1950); cf. preceding abstract.]*

No significant amounts of phenyllactic acid were found in the serums of 18 patients with phenylpyruvic oligophrenia. The free phenylalanine (I) concentrations of the serum were 19–38 mgm. per cent. No correlation was found between the degree of mental deficiency and the serum (I) concentration. Spinal fluid contained 6·1–8·2 mgm. per cent. of (I). It is suggested that although the increased amount of (I) is a result of metabolic error, its blood plasma level is determined by the ability of the kidney tubules to reabsorb (I). *Cf. C. A.*, **44**, 2590d.

L. E. Gilson (Chem. Abstr.).

*Surface Tension of Spinal Fluid and the Phenomenon of "Antagonism." Piccardi, G., and Ferroni, E. (Univ. Florence, Italy). [Sperimentale, Sez. chim. biol. (**1**), 181–8 (1950).]*

The surface tension of 2·5 c.c. spinal fluid poured on a watch glass was measured before and after addition of Na oleate. Following the known drop and "antagonistic" recovery of the dynamic surface tension three sharp minima in the curve were observed. Since a solution of trimethylcellulose (0·5 per cent.) gave minima similar to those of the spinal fluid, it is concluded that the phenomenon is due to the Na oleate. The minima are similar to those observed by Lecomte du Nouy by determining the tension as a function of dilution. Theory: The Na oleate is adsorbed on internal surfaces of the colloid.

A. E. Meyer (Chem. Abstr.).

*The Proteins and the Hydrochloric Acid-collargol Reaction of the Cerebrospinal Fluid. Pérez-Tores, A., and Fontán J. L. Rivero. (Univ. Seville, Spain). [Rev. clín. españ., **35**, 111–20 (1949).]*

Spinal fluid from normal subjects and from patients with various types of meningitis and some miscellaneous diseases was examined. The amount of each protein fraction was determined by known methods and the HCl-collargol reaction of Riebeling (*C. A.*, **32**, 5488[5]) was applied. The shape of the curve obtained varied with the protein make-up of the fluid, especially with the relative, and at

times absolute increase in euglobulins, and less frequently with the shift in the proportions of pseudoglobulin (I) and (II) present. The value of these determinations as an aid to diagnosis is discussed. L. E. Gilson (Chem. Abstr.).

The Indican Content of Cerebrospinal Fluid in Physiological and Pathological Conditions. Tinelli, Guiseppe (Univ. Bari, Italy). [*Policlinico (Rome), Sez. med.*, **52**, 69–78 (1945).]

By the Bohm and Gruner method (*C. A.*, **30**, 6404[6]) it was found: Normal subjects (20 cases), averaged 23·7γ per cent. (variations probably according to age); patients with nervous diseases (32 cases), meningitis (19 cases), nervous syphilis (11 cases), and metasyphilis (19 cases), respectively, 50·6, 56·7, 67 and 67·5γ per cent. Indican increase is due to both an increased passage from the blood to the cerebrospinal fluid through the altered blood-cerebrospinal barrier and to biochemical processes (protein fission) occurring in the same cerebrospinal fluid.
C. Scandura (Chem. Abstr.).

Examination of Cerebrospinal Fluid and Blood. Simplified Methods Derived from the Quantitative Gold Reaction. Lange, Carl, Miller, John K., and Harris, Albert H. (New York State Dept., Health, Albany). [*Am. J. Clin. Path.*, **20**, 872–6 (1950).] John T. Myers (Chem. Abstr.).

The Cerebrospinal Fluid in Multiple Sclerosis. Freedman, David A., and Merrit, H. Houston (Tulane Univ., New Orleans). [*Proc. Assoc. Research Nervous Mental Diseases*, **28**, 428–39 (1950).]

Review, with general discussion of chemical mechanism of colloidal reactions of cerebrospinal fluid. Warren M. Sperry (Chem. Abstr.).

Changes of Functional State of the Nervous System in Protein Deficiency. Dinerman, A. A., and Semenova, G. T. (1st Med. State Inst., Moscow). [*Arkh. Patol.*, **12**, No. 4 62–8 (1950).]

In rats protein starvation causes a severe instability of chronaxia analogous to that observed clinically in dystrophy. Caloric deficiency with full protein requirement alters chronaxia but slightly. The results are reversible by full diet.
G. M. Kosolapoff (Chem. Abstr.).

Carbonic Anhydrase in the Brain of the Newborn in Relation to Functional Maturity. Ashby, Winifred, and Schuster, Ernest M. (St. Elizabeth Hospital, Washington, D.C.). [*J. Biol. Chem.*, **184**, 109–16 (1950); *cf. C. A.*, **43**, 4747*d*).]

Carbonic anhydrase appeared late in the cerebrum of the young of the dog, cat, rat and rabbit, but was present at birth in the young of the guinea-pig and cow, which are more mature when born, suggesting a correlation between the appearance of the enzyme in the cerebrum and the beginning of its functioning.
George K. David (Chem. Abstr.).

Effect of Acute Hypoxia on the Motor Cells of the Spinal Cord. Krogh, Erik (Univ. Aarhus, Denmark). [*Acta Physiol. Scand.*, **20**, 263–92 (1950).]

Experiments were made on rabbits. Hypoxia was produced by clamping off aorta for varying lengths of time. Spasticity was examined electromyographically. The hyperactivity of the muscles of the lower extremities observed in hypoxemic rabbits is due to the preserved large motor cells in the anterior horn. In nearly every case these cells were found to be normal physiologically, but more chromophobic than in normal rabbits. The swollen, extremely chromatolytic cells are acutely degenerating cells which are dying following a stage of hyperactivity. The dead nerve cells disappear after 48–60 hours. Anoxemia damages more seriously neurons in the center of the anterior horn. S. Morgulis (Chem. Abstr.).

Do Adrenergic Vasodilator Nerves Exist? Folkow, Björn, and Uvnas, Börje (Univ. Lund, Sweden). [*Acta Physiol. Scand.*, **20**, 329–37 (1950).]

From point of view of chemical transmission, sympathetic vasodilator nerves are cholinergic and adrenergic. Experiments on the action of atropine and eserine

on vasodilator responses to stimulation show that skeletal muscles (cat) are supplied with sympathetic vasodilator fibers of cholinergic type. The existence of adrenergic vasodilator fibers is questioned, and it is suggested that this chemical transmission is exclusively cholinergic. Furthermore, since atropine completely annuls the vasomotor responses to stimulation of sympathetics while neo-antergan, even in doses which strongly antagonize the vasodilator action of histamine, produces no blocking, the hypothesis of the existence of vasodilator fibers of an histaminergic type in the sympathetic outflow finds no support. S. Morgulis (Chem. Abstr.).

Sympathicomimetic Action of Brain Extracts. Holtz, Peter (Karolinsches Inst., Stockholm). [*Acta Physiol. Scand.*, **20**, 354–62 (1950).]

By two sensitive tests (blood pressure in cat and uterus of the rat), the sympathicomimetic action of brain extracts (beef, rabbit) was differentiated into adrenaline and arterenol actions. In both animals the two substances are present approximately in the same proportion (90 per cent. arterenol, 10 per cent. adrenaline), but whereas beef brain yields about 0·2γ the rabbit brain yields 2γ. Cocaine increases the pressor action of the extracts to the same extent as it does that of arterenol.

S. Morgulis (Chem. Abstr.).

Survival and Revival of Nervous Tissues after Arrest of Circulation. Heymans, C. (Univ. Ghent, Belg.). [*Physiol. Rev.*, **30**, 375–92 (1950).]

Nervous tissue is more sensitive to lack of O and, therefore, to interruption of blood supply than are other tissues, and not all parts of the nervous system are equally affected ; all can withstand complete anoxia up to five minutes, and none can survive more than 30 minutes. Within this time limit the survival is in this diminishing order : Respiratory, vasomotor or cardioregulatory center > palpebral pupillary centers > cortical centres. Sudden circulatory arrest may be treated by cardiac massage in case of cardiac standstill, or in case of ventricular fibrillation by electric shock, or by injection of procaine-HCl into the blood stream.

S. Morgulis (Chem. Abstr.).

Effect of Partial Extirpation of Adrenals on the Higher Nervous Activity in Dog. (II) One-day Fast, Caffeine and Muscular Labor. Gzgzyan, D. M. (Pavlov Evolut. Physiol. Inst., Acad. Med. Sci., U.S.S.R.). [*Fiziol. Zhur.*, **36**, 261–70 (1950) ; *cf. ibid.*, **35**, 637 (1949).]

After partial removal of adrenals a one-day fast taking place in the most distinct period of changes of neural activity (2nd phase) causes a decline of conditioned reflexes, while unconditioned reflexes are stimulated. In the restorative phase after the operation, a one-day fast gives the same reactions as in controls. Feeding of caffeine in various doses leads to increased sensitivity to the drug. Light labor lowers, hard labor raises the level of stimulation of the central nervous system.

G. M. Kosolapoff (Chem. Abstr.).

Nucleic Acids of the Brain during Prolonged Protein Starvation. Mandel, Lila, Jacob, Monique, and Mandel, Paul (Univ. Strasbourg, France). [*Compt. rend. soc. biol.*, **144**, 275–6 (1950) ; *cf. C. A.*, **44**, 8438*a*).]

L. E. Gilson (Chem. Abstr.).

Signal Transmission in Nerve. Muralt, Alexander v. (Univ. Bern., Switz.). [*Harvey Lectures, Ser.* **43**, 230–53 (1947–48).]

The conduction of the nervous impulse was studied by three approaches, i.e. the electric, the chemical, and the internal organization. The excitation wave is transmitted in jumps from one node to the next in medullated nerves. This method increases the speed of conduction. The internode is essential for the electrotonic spread of the stimulus. The newborn action potential is produced at the neighbouring node, and then jumps by spatial conduction from node to node. The production of the action current is derived from chemical reactions, and is accompanied by the release of acetylcholine and a thiamine compound. The internode is probably the locus for the production of free energy to the sites of excitation. From the cell body a nutritive influence is exerted which maintains the internal organization of the whole nerve and produces regeneration after injury.

Julia O. Holmes (Chem. Abstr.).

Properties of Preparations from the Central Nervous System which Degrade Coenzymes (I) and (II); their Connection with Carbohydrate Metabolism. H. McIlwain (Maudsley Hosp., London). [*Biochem. J.*, **46**, 612–19 (1950).]

Phenosafranine (I) is a very potent inhibitor of cozymase degradation. Janus Green is another phenazine derivative which is very potent. (I) increases aerobic glycolysis of brain cortex almost to the anaerobic level without exerting much effect on respiration. (I) is now shown to be the most potent of phenazone compounds inhibiting degradation of cozymase. Nicotine, and even more so the structurally related compound, 4-(3-pyridyl)-4H-isoimidazole inhibit cozymase degradation. Although all substances inhibiting cozymase degradation release aerobic glycolysis, many do so without effect on cozymase degradation (KCl, CO, guanidines and amidines). Though it is not known whether continual breakdown and resynthesis of cozymase is involved in the reactions of carbohydrate metabolism and utilization in tissues, it is very probable that the enzyme, isolated from mammalian brain or spinal cord by extraction with H_2O or strong salt solutions, which degrades cozymase does play a specific role in carbohydrate metabolism in the brain. It is suggested that this may operate through the mechanism of phosphorylation which normally accompanies oxidation. S. Morgulis (Chem. Abstr.).

Concentration or Exclusion of Some Heterocyclic Compounds by Brain Cortex, in Relation to Their Effects on Cardohydrate Metabolism. McIlwain, H., and Grinyer, I. (Maudsley Hosp., London). [*Biochem. J.*, **46**, 620–8 (1950).]

Some pyridine and phenazine derivatives which disturb the balance of carbohydrate and metabolism in slices of brain cortex also inhibit degradation of cozymase. The object was to find the concentrations at which these substances act upon each process separately. Slices of guinea-pig cortex absorb phenosafranine, diazine green, neutral red, and ethyl red from a glucose-saline medium aerobically until the concentration in the slice is 50–300 times greater than in the medium. Nicotine and nicotinamide are largely excluded from the slices. The absorption (max. rate about 1 micromole/g moist tissue wt./hr.) is greater aerobically with glucose than anaerobically and without glucose, the continued glucose metabolism being necessary for the tissue to hold phenazine or quinoline derivatives to the maximum extent. The substances increase aerobic glycolysis in concentrations which have no or little effect on respiration, while those which do not increase glycolysis have no or little action on cozymase degradation. Those of the former type have an unsubstituted pyridine N, and in the three position a substituent including the group $R_1R_2C–NHR_3$. The most active phenazine derivatives have basic substituents at 3 and 6, and a N-phenyl group. The concentrations of phenosafranine, diazine green, and neutral red (phenazine); ethyl red (quinoline) and nicotine and nicotinamide (pyridine) needed to increase aerobic glycolysis to a selected value and their effects on cozymase degradation are tabulated.
S. Morgulis (Chem. Abstr.).

Mechanism of Inhibition of Anaerobic Glycolysis of Brain by Sodium Ions. Utter, M. F. (Western Reserve Univ., Cleveland, Ohio). [*J. Biol. Chem.*, **185**, 499–517 (1950); *cf. Racker and Krimsky, C. A.*, **40**, 1932.[3]]

The cord and medulla of cotton rats and the remaining brain tissue were homogenized separately, and extracts were prepared by centrifuging. Manometric studies were carried out in Warburg vessels, and individual enzymes of the glycolytic system were investigated in Thunberg tubes. Inhibition of acid production by Na in the presence of brain homogenate was strong when glucose was the substrate, but only slight when hexose diphosphate (I) was used. Even in the presence of (I), Na prevented utilization of inorganic phosphate and decreased that of glucose by both brain and cord homogenates. The effect on extracts was less marked. Inhibition was pronounced at a Na concentration of 0·035 M, and it increased rapidly with increasing concentration. High concentrations of K and Li were also inhibitory, as were low concentrations of Ca (0·02 M) and sulfate ion (0·04 M). The presence of Na had no effect on hexokinase, phosphohexokinase, or the coupled oxidation-phosphorylation reaction, but strongly inhibited the transfer of phosphate from phosphopyruvate to adenylic acid. Fred H. Snyder (Chem. Abstr.).

Cerebral Anoxia in Infantile Dehydration. Kerpel-Fronius, E., Varga, F., and Kun, K. (Univ. Children's Clinic, Pecs, Hung.). [*Arch. Disease Childhood*, **25**, 156–8 (1950).

The O_2 saturation of the blood of the longitudinal sinus was determined in 11 dehydrated infants. It decreased parallel to the gravity of the clinical condition. A close inverse correlation was found between the decrease of the O_2 saturation of the cerebral venous blood and anhydremic shock as measured by circulation time. Cerebral symptoms characteristic of a toxic condition in dehydration appeared when the O_2 saturation of the cerebral venous blood approached 25 per cent. Deep coma was observed when the latter decreased to less than 15 per cent. Thus, the cerebral symptoms of severe dehydration appear to be due to cerebral anoxia of the stagnating type. KATHRYN KNOWLTON (Chem. Abstr.).

The Vegetative Nervous System and Blood-sugar Regulation. Simon, Kurt (Med. Akad., Dusseldorf, Ger.). [*Klin. Wochschr.*, **28**, 152–8 (1950).]

Results of tests show that all patients with acute illness within the cerebrum or cerebellum showed a reversal in curves from the expected norm after the administration of adrenaline as well as after the administration of insulin. The height of the paradoxical blood-sugar rise after the administration of insulin was dependent on the severity of the disease and on the rapidity of appearance of symptoms of cerebral damage. After improvement in condition the blood-sugar curve began approaching normal. After the brain injury had healed completely adrenaline and insulin injections yielded a normal blood-sugar curve.

RENATE H. MEDVED (Chem. Abstr.).

Cephalinase in Nervous Tissue. Tyrrell, L. W. (Whitchurch Hosp., Cardiff, Wales). [*Nature*, **166**, 310 (1950).]

A process is given whereby the P turnover rate in brain phospholipides is shown to occur mainly in the cephalin fraction. This is attributed to the possible presence of cephalinase which has little or no effect to the lecithin portion. Work was carried out on sterile rat brain tissue buffered at pH 7·5 and incubated at 37°.

A. B. S. (Chem. Abstr.).

The Chemistry of Myelination and Demyelination. Sperry, Warren M., and Waelsch, Heinrich (N.Y. State Psychiat. Inst., New York, N.Y.). [*Proc. Assoc. Research Nervous Mental Diseases*, **28**, 255–67 (1950).)]

Review. W. M. S.

The Behaviour of Potassium and Calcium in the Blood Serum in Epilepsy. Weinland, Wolf L. (Anstait, Bethel Bielefeld, Ger.). [*Arch. Psychiat. Nervenbrankh.*, **183**, 731–8 (1950).]

K was determined 522 and Ca 489 times in the blood of 128 epileptics before, during, and after seizures. The results showed no definite relation between the concentrations of K and Ca, and the occurrence of epileptic seizures.

The Evaluation of Cerebral Processes by the Intravenous Insulin Functional Test of V. Falkenhausen and Gaida. Reiss, Ernest (Landeskrankenhaus, Detmold, Ger.). [*Deut. Z. Nervenheilk.*, **164**, 303–16 (1950).]

The blood-sugar concentration (I) curve after insulin administration under standardized conditions was determined 172 times in 83 patients with various types of cerebral disease. The abnormal types of response were, no change in (I), a decrease in (I) without subsequent rise, and an increase in (I) without subsequent decrease during the 200 min. of observation. The abnormal responses are related to disturbances in the function of the hypophysis and hypothalamus.

WARREN M. SPERRY (Chem. Abstr.).

The Incidence and Significance of Hypoglycemia in Unselected Admissions to a Psychosomatic Service. Landmann, H. R., and Sutherland, R. L. [*Am. J. Digestive Diseases*, **17**, 105–8 (1950).]

A 5-hour glucose tolerance test was performed on 50 consecutive patients admitted to a psychosomatic service after a few days of well-balanced diet. Blood

Ca and protein levels also were determined. In 44 per cent. of cases the blood sugar fell to hypoglycemic levels (below 70 mgm. per cent.) during the tolerance test. In 14 per cent. of cases there was a delayed insulin response.

W. E. C. (Chem. Abstr.).

Phosphatase of Brain Tissue. Binkley, Francis, and Olson, C. K. (Univ. of Utah, Salt Lake City). [J. Biol. Chem., **186**, 725–30 (1950).]

A phosphatase (I) in purified condition was isolated from pig brain. This enzyme completely hydrolyzes inorganic pyrophosphate, and after 90 minutes' incubation removes approximately 50 per cent. of the terminal phosphate from adenosinetriphosphate. Preinoculation of (I) with Mg^{++} ions + glutathione (II) was more effective than preincubation with (II) alone. Prolonged preincubation with Mg^{++} ions made (I) about 55 per cent. as active as preincubation with (II) + Mg^{++} ions. The activity of (I) is dependent upon the concentration of Mg^{++} ions between 0·0025 to 0·01 M; higher concentrations cause inhibition. Of other metals tested, only Mn^{++} ions + (II) exhibited an activating effect upon (I).

Lawrence Rosen (Chem. Abstr.).

Role of Glutamic Acid in the Transport of Potassium in Brain and Retina. Terner, C., Eggleston, L. V., and Krebs, H. A. (Univ. Sheffield, Engl.). [Biochem. J., **47**, 139–49 (1950).]

Slices of brain cortex (guinea-pig, rabbit) lose K ions by diffusion into the saline medium except under aerobic conditions and in the presence of both glucose and L-glutamate. Similarly retinas (ox eye) stored at 0° for 1–2 hours exchange nearly 50 per cent. of the K for Na, but the ionic concentrations are more or less restored during incubation provided both glucose and L-glutamate are present in the medium. However, the glucose could be replaced with lactic or pyruvic acid and the L-glutamate by L-aspartate. Since the latter is converted in brain or retina to glutamate, it is doubtful if the effect on K-ion diffusion is affected by the aspartate. Under anaerobic conditions glucose and glutamate have no significant influence on the K content of brain slices. It seems probable that while L-glutamate participates in the K transport, the glucose (or lactic and pyruvic acid) serve as sources of energy.

S. Morgulis (Chem. Abstr.).

The Cerebral Blood Flow in Male Subjects as Measured by the Nitrous Oxide Technique. Normal Values for Blood Flow, Oxygen Utilization, Glucose Utilization and Peripheral Resistance, with Observations on the Effect of Tilting and Anxiety. Scheinberg, Peritz, and Stead, Euegne A. (Duke Univ., Durham, N.C.). [J. Clin. Invest., **28**, 1163–71 (1949).]

The N_2O method was used for measuring cerebral blood flow in 20 normal young men in the supine position. In normal resting subjects 14 per cent. of the cardiac output is devoted to the cerebral circulation and 22 per cent. of the total O consumption is cerebral. Anxiety made no difference in cerebral metabolic function. Tilting normal subjects to the erect position caused a 21 per cent. fall in cerebral blood flow, a 23 per cent. fall in cerebral arterio-venous O difference, a 34 per cent. fall in effective arterial pressure, and a 10 per cent. fall in cerebral vascular resistance. Cerebral O utilization is relatively constant in the normal person under ordinary stresses. Its buffer system is flexible, allowing the cerebral arterio-venous O difference to compensate for relatively large changes in cerebral blood flow.

John T. Myers (Chem. Abstr.).

Change of Nitrogen Metabolism in Spinal Cord of Rabbits in Diphtheria. Promyslov M. Sh. (Doklady Akad., Nauk, S.S.S.R., **73**, 775–7 (1950); *cf. C. A.,* **44**, 2107*h*).]

The character of N metabolism in the spinal cord of rabbit is of the same type as that of the brain proper. The extent of decomposition of N-containing substances increases exclusively at the expense of proteins, while metabolism of N-containing lipides is unaltered. Protein N declines in diphtheria, while residual N rises. H_2O content rises in the spinal cord, but drops in the brain.

G. M. Kosolapoff (Chem. Abstr.).

The Relation of the "Hydergin-glucose-test" to Psychic and Physical Status. Solma, Hugo (Psychiat. Clinic, Univ. Basel, Switzerland). [*Schweiz. Arch. Neurol. Psychiat.*, **65**, 311–29 (1950) (in *German*); *cf. C. A.*, **38**, 4600[6]).]

Glucose (I) tolerance was determined in 28 normal human subjects without, and 1 or 2 days later with, the intravenous injection of 0·3 mgm. hydergin (II), a mixture of DHO, DCS and DHK. (II) was given at the same time as the 20 g. dose of (I). (II) usually inhibited the rise in blood (I) concentration, but to a widely variable degree which was related to physical and psychic status. In subjects of the pyknic type the inhibition was less than in those of the leptosomic-asthenic type. In subjects with a passive psyche the inhibition was large, and in those with an active, vital psyche it was small.

WARREN M. SPERRY (Chem. Abstr.).

Biochemical Studies on the Action of the Nerve. (I) The Distribution of Cholinesterase in the Human Brain. Okinaka, Shigeo, Yoshikawa, Masaki, and Goto, Juya (Univ., Tokyo). [*Igaku to Seibutsugaku (Med. and Biol.)*, **17**, 82–5 (1950).]

Cholinesterase activities were determined in various parts of human brain by the method of Ammon (*C. A.*, **28**, 1724[8]). The results obtained agreed well with those by Nachmansohn (*C. A.*, **33**, 7322[8]).

MICHINORI NAKAMURA (Chem. Abstr.).

Brain Concussion and Blood Sugar. Mate, Istvan (Tudomanyegyetemi III, sz. Sebeszeti Klinika, Budapest, Hung.). [*Orvosi Hetilap*, **89**, 414–16 (1948).]

The blood sugar level was determined on 42 persons with brain concussion (I). In 9 cases this value was 140–160 mgm. per cent. Then a load was applied by dosing perorally 50 gm. dextrose. The sugar content of blood was determined every 30 minutes for 3 hours. Persons suffering from (I) showed blood sugar of 210–350 mgm. per cent. Persons showing normal blood sugar were free from (I). Blood-sugar values approached normal with disappearance of (I). The actual increase of blood sugar was not in proportion to the gravity of (I).

ISTVAN FINALY (Chem. Abstr.).

Biochemical Studies in Multiple Sclerosis. Jones, Harold H., Jones, Harold H., jun., and Bunch, Leitha D. (Winfield, Kan.). [*Ann. Internal Med.*, **33**, 831–40 (1950).]

In multiple sclerosis there is an abnormal response to oral glucose, the most striking evidence of which is blood elevation of pyruvic acid out of proportion to lactic acid. In cases in relapse, the fasting level of pyruvic acid is high and remains so throughout a glucose tolerance test. If the disease is less active, the disproportion of pyruvic to lactic acid does not appear until the 2nd, 3rd and 4th hour after glucose administration. Serum cholesterol is elevated and is higher in the active than in the quiescent case. Serum inorganic P level is low and P excretion is low when compared with urinary preformed creatinine, but after giving glucose urinary excretion of P is increased over the fasting state by 72, 24 and 25 per cent. at the 2nd, 3rd and 4th hours as compared to decrease of 31, 41 and 36 per cent. in controls. The urinary uric-acid creatinine ratio after glucose is lower than normal, being little different from the fasting level throughout the test.

JOHN T. MYERS (Chem. Abstr.).

Cerebral Blood Flow and Oxygen Consumption in Neurosyphilis. Patterson, John L. jun., Heyman, Albert, and Nichols, Fenwick T., jun. (Harvard Med. School, Boston, Mass.). [*J. Clin. Invest.*, **29**, 1327–34 (1950).]

Cerebral O consumption (CMRO), vascular resistance (CVR), and cerebral blood flow (CBF) were determined by the nitrous oxide method in 58 patients with neurosyphilis and in 16 controls. In patients with dementia paralytica, the CBF and CMRO were reduced, and the mean CVR was increased. There was a definite relation between mental deterioration and reduction in CMRO.

JOHN T. MYERS (Chem. Abstr.).

2. Pharmacology and Treatment.

Pharmacological Action of β-phenylisopropylamine on the Nervous System. III. Action on Convulsive Activity in Cortical Motor Neurones. Scavinci, V. (Univ. Bologna, Italy). [*Boll. soc. ital. biol. sper.*, **25**, 217–19 (1949); *cf. C. A.*, **44**, 740*d*, 3141*a*.]

A 2 per cent. solution of β-phenylisopropylamine applied to the motor cortical zone in the dog, causes lowering of faradic excitability; a stronger (5 per cent.) solution has the optimum effect. Four medium-sized dogs were morphinized (thus suppressing all epileptic reflexes) and treated with the drug. Circumscribed application of the 2 per cent. drug, followed by stimulation of the cutaneous contralateral reflex area, gave a typical clonic reaction which persisted during the hyperactivity of the cortex. The details of the effects are given. The drug appears to excite cortical hyperactivity, which causes corticifugal convulsions. Possibly the convulsions are really present before the peripheral effects, but the corticifugal action may be affected by the spinal motorneurones, and thus cannot produce a motor effect. While convulsive activity is reinforced by a corticipetal impulse due to stimulation of the skin, the corticifugal effects may produce a motor response.
B. A. (Chem. Abstr.).

Glutamic Acid in the Treatment of Mentally Handicapped Children. A Review of the Background. Clapp, Roger W. (St. Louis Univ., St. Louis, Mo.). [*J. Missouri State Med. Assoc.*, **46**, 181–2 (1949).]

Biochemical, animal and clinical experiments suggesting that the administration of glutamic acid in large doses be used to improve mentally handicapped children and so facilitate teaching, are reviewed. Results of the administration of this substance to mentally dull children suggested that it is indicated only as an adjunct to teaching. RUTH BERGGREN (Chem. Abstr.).

Effect of Narcotics on Cell Respiration. Issekutz, B., jun., Lichtneckert, I., and Hetényi, G., jun. (Univ. Szeged, Hung.). [*Arch. intern. pharmacodynamie*, **83**, 33–48 (1950).]

Phenobarbital diluted to 2×10^{-3} decreases the O_2 uptake of surviving rat kidney slices and diaphragm by about 20 per cent. and inhibits the action of dinitrophenol on frog muscle, but urethan, morphine and scopolamine do not. The two last named cause some increased activity. In dogs, tissue respiration *in vivo* was not decreased by any of these drugs. M. L. C. BERNHEIM (Chem. Abstr.).

The Neuromuscular Blocking Action of Succinylcholine (Diacetylcholine). Castillo, Julio C., and De Beer, Edwin J. (Wellcome Research Labs., Tuckahoe, N.Y.). [*J. Pharmacol. Exptl. Therap.*, **99**, No. 4, Pt. 1, 458–64 (1950).]

Succinylcholine resembles 2 molecules of acetylcholine linked together at the α-Me groups. It possesses the maximum neuromuscular blocking activity of its homologous series. It has 10 atoms (8C and 2O) interposed between the 2 quartenary N atoms, and thus approaches the favourable chain length found in decamethonium bromide. It exhibits a strong neuromuscular blocking action in the cat, rabbit and mouse, but the paralysis is of relatively short duration. The action is greatly prolonged by eserine. L. E. GILSON (Chem. Abstr.).

Effect of Insulin Hypoglycemia on Eosinophiles and Lymphocytes of Psychotics. Tsai, Shih Yuan, Bennett, Alene, May, Lawrence G., and Gregory, Raymond L. (Univ. of Texas Med. School, Galveston). [*Proc. Soc. Exptl. Biol. Med.*, **74**, 782–4 (1950).]

Insulin hypoglycemia causes in schizophrenics a significant eosinopenia and lymphocytopenia, which are considered to be indicative of adrenocortical stimulation. Insulin does not produce such changes if hypoglycemia is prevented by glucose administration. L. E. GILSON (Chem. Abstr.).

Action of Phenamine on the Higher Nervous Activity in the Dog. Pavlov, B. V. (Pavlov Physiol. Inst., Acad. Sci. U.S.S.R.). [*Fiziol. Zhur.*, **36**, 271–82 (1950).]

Feeding 0·0025–0·5 mgm./kgm. phenamine 25–60 minutes before the experiments in which noises, light or touch stimuli were used for investigation of reflex activity in dogs, showed that 0·06 mgm. dosage gives optimum results in dogs with a weak nervous organization, while maximum doses are best for the better organized animals. These doses gave significant increase of conditioned salivary reflexes. The latent period was shortened in all cases. Under the action of the drug dogs which were normally restless in sound-proof boxes became quiet. Pulse rate usually rose, as did respiration. Frequent repetition of the drug eventually led to sharp reflex decline and refusal of food.

G. M. Kosolapoff (Chem. Abstr.).

Neuromuscular Excitation: Responses of Normal and Denervated Mammalian Muscle to Bis (Trimethylammonium) Decane (C_{10}) and to d-Tubocurarine. Jarcho, L. W., Eyzaguirre, C., Talbot, S. A., Lilienthal, J. L., jun., and Leakins, E. (Johns Hopkins Univ., Baltimore, Md.). [*Am. J. Physiol.*, **162**, 475–88 (1950); *cf. C. A.*, **43**, 2329*e*.]

Bis (trimethylammonium) decane (C_{10}) depresses markedly the twitch tension of innervated rat muscle and causes asphyxial death unless respiration is artificially maintained. C_{10} reduces end-plate potential below the amplitude necessary for initiation of a prolonged electrical response in muscle fibers. C_{10} also reduces strength of contraction of denervated muscles stimulated directly; this action is blocked by *d*-tubocurarine. In both innervated and denervated muscle C_{10} depresses demarcation potentials. This action is also blocked by *d*-tubocurarine. Fibrillation potentials of denervated muscle are obliterated by C_{10} and partially suppressed by *d*-tubocurarine. It is suggested that both drugs are active at the motor end plate and also at undefined regions along the muscle fiber.

E. D. Walter (Chem. Abstr.).

Narcotics and the Phosphates of Brain. Buchel, L., and McIlwain, H. (Univ. of London). [*Nature*, **166**, 269–70 (1950).]

Chloral and ethylbutylbarbituric acid cause a fall in cerebral respiration in guinea-pig cortex slices *in vitro* accompanied by a fall in phosphocreatine, and an increase of inorganic phosphate. Wesley H. Hartung (Chem. Abstr.).

The Relation Between the Elicitation of Convulsions and the Inhibition of the Enzymic Decomposition of the Active Substance of Sensory Nerve Fibers by Several Drugs. Hellauer, H. F., and Umrath, K. (Univ. Graz, Austria). [*Z. Vitamin-Hormon- u. Fermentforsch*, **3**, 244–9 (1950) (*in German*); *cf. C. A.*, **43**, 5842*d*.]

The dilutions required to elicit convulsions in frogs were: strychnine (I) 1 : 1:10,000, picrotoxin (II) 1 : 4,000, brucine (III) 1 : 500, cardiazole (IV) 1 : 200. The dilutions required for complete inhibition of the enzymic decomposition of the sensory nerve fiber agent were: (I) 1 : 10,000, (II) 1 : 2,000, (III) 1 : 1,000, (IV) 1 : 250. The dilutions required for complete inhibition of cholinesterase, on the other hand, were: (I) 1 : 3,000, (II) 1 : 300, (III) 1 : 300, (IV) 1 : 500. This proves a relationship between the inhibition of the enzymic breakdown of the sensory nerve fiber agent, but not of acetylcholine, and the elicitation of convulsions. Simultaneous inhibition of cholinesterase by eserine affects the nature of the convulsions. Erich Hirschberg (Chem. Abstr.).

Evaluation of Curarizing Agents in Man. Unna, K. R., Pelikan, E. W., Macfarlane, D. W., Cazort, R. J., Sadove, M. S., and Nelson, J. T. (Univ. of Illinois, Coll. of Med., Chicago). [*J. Am. Med. Assoc.*, **144**, 448–54 (1950); *cf. C. A.*, **44**, 6517*d*.]

Two synthetic compounds with curare-like action, decamethonium bromide (I) and flaxedil (II) have been tested under a variety of conditions. (I) measured by its effect on grip strength, surpasses tubocurarine chloride (III) or (II) in potency. The different drugs have three different thresholds to paralyzing effects on the

respiratory muscles, being lowest for (I) and highest for (II). The duration of the effect is longest for (III), and shortest for (II). Unlike the tubocurarine preparations, the effect of (I) is not cumulative. No antidote to (I) is known, while neostigmine methyl sulfate mitigates the effects of a subsequent injection of (III). Pretreatment with (III) greatly reduces the curarizing effects of subsequent injections of (I). S. Morgulis (Chem. Abstr.).

Blood-sugar Curve in Electroshock. Valerio, Valerio, and Cataldi, Luigi (Univ. Naples). [*Riforma med.*, **64**, 606–8 (1950).]

Within 10 to 30 minutes after initiation of shock treatment the blood sugar increases to a peak that corresponds to clinical hyperglycemia. A gradual fall to normal is succeeded after 3·5 hours by hypoglycemia that lasts to the end of treatment. A. E. Meyer (Chem. Abstr.).

The Mode of Action of Myanesin on the Central Nervous System. Henneman, Elwood, and Scherrer, Jean. [*Trans. Am. Neurol. Assoc.*, **74**, 208–11 (1949).]

Marion Horn Peskin (Chem. Abstr.).

The Anti-convulsant Action of 2,2-Diethyl-1, 3-Propanediol and Some of its Homologs and Esters. Berger, F. M., and Ludwig, B. J. (Mount Labs., Inc., New Brunswick, N.J.). [*J. Pharmacol. Exptl. Therap.*, **100**, 27–37 (1950); *cf. C. A.*, **43**, 8546g.]

2,2-diethyl-1,3-propanediol (I) strongly antagonizes the convulsant and lethal effects of metrazole, strychnine and picrotoxin. These antagonistic effects occur with doses which do not exert a hypnotic or anesthetic action. (I) can be effectively administered enterally or parenterally. Its duration of action is short. (I) does not affect spinal reflexes and has little action on the spinal cord. It acts by a depressant effect on the forebrain and midbrain. (I) is partly conjugated in the body as an ether type glucuronide. Another portion is oxidized to α,α-diethylhydracrylic acid (II). The further oxidation product, diethylmalonic acid (III) was not found in the urine of patients receiving (I). (II) and (III) in doses of 400 mgm./kgm. had no anti-convulsant action. The 2,2-dimethyl, 2-methyl-2-ethyl, 2-methyl-2-propyl, 2-methyl-2-isopropyl, 2-methyl-2-butyl, 2-ethyl-2-butyl, 2-ethyl-2-phenyl, 2,2-dipropyl and 2,2-dibutyl homologs of (I) showed an anti-convulsant activity of a similar order to that of (I). None had a longer duration of action. (I) diacetate had a less intense but more prolonged action than (I). (I) monoacetate, succinate and dibenzoate showed no advantage over (I).

L. E. Gilson (Chem. Abstr.).

Anti-convulsant Properties of Benadryl and Pyribenzamine. Swinyard, Ewart A., Jolley, Joel M., and Goodman, Louis S. (Univ. of Utah, Salt Lake City). [*Proc. Soc. Exptl. Biol. Med.*, **75**, 239–42 (1950).]

Benadryl, pyribenzamine and dilantin all protected rats to a certain extent against electroshock convulsions, but had no preventive action against metrazole-induced convulsions. L. E. Gilson (Chem. Abstr.).

The Action of Hexachlorocyclohexane on the Central Nervous System (Warm-blooded Animals). Herken, Hans (Freie Univ., Berlin). [*Klin. Wochschr.*, **28**, 582–4 (1950).]

Aqueous suspensions of γ-hexachlorocyclohexane inhibit metrazole cramps in rats. The β-isomer postpones the onset of the cramps, while the α-isomer had no effect. In paraffin solution less cramp inhibition is experienced. Strychnine tetanus was prevented in some animals with gammexane. One large dose has more effect than several small ones, which points to an allobiotic action.

Dorit L. Noether (Chem. Abstr.).

The Spasm-preventing Effect of Histamine and Nicotinic Acid on Experimental Human Convulsions. Kajtor, Ferene (Univ. Debrecen, Hungary). [*Kiserletes Orvostudomany*, **2**, 206–17 (1950).]

Intravenous injections of 1·1–2·4 mgm. histamine (I) inhibited metrazole convulsions, but they were without effect against convulsions caused by electric

shock. Nicotinic acid, nitroglycerine and adrenaline showed no preventive effects. The inhibiting effect of (I) was proportional to the dose and lasted for about 40 seconds. The simultaneous administration of (I) with metrazole inhibited convulsions ; (I) was ineffective when given more than 40 seconds after the injection. The inhibiting effect of (I) is explained by the direct action on the nerve cells or through the autonomic nervous system. Acetylcholine bromide, carbamylcholine and amyl nitrite showed spasm-preventing effects similar to (I), but much weaker.
I. FINALY (Chem. Abstr.).

Lethal Barium Chloride Poisoning with Special Reference to Changes in the Cerebral Tissues. Fazekas, I. Gyula. [*Orvosi Hetilap*, **90**, 280–3 (1949).]

In 4 cases of poisoning from administration of 7 to 20 gm. $BaCl_2$, death occurred in 4·5–23 hrs. after intake. Severe changes occurred in the tissues of the central nerve system. ISTVAN FINALY (Chem. Abstr.).

Pharmacology of the Nerve System Regulating Metabolism. Issekutz, Bela, sen., and Issekutz, Bela, jun. [*Orvosi Hetilap*, **90**, 257-63 (1949).]

Benzedrine phosphate, pulsoton, ephedrine and thyroxine increase the gas metabolism by excitation of the metabolism centers belonging to the sympathetic nerve system. This effect may be stopped by hypothalamic hypnotics, especially by morphine, scopolamine and dihydroergocornine. These latter agents were ineffective against adrenaline and 2,4-dinitrophenol, which directly increased cell oxidation. ISTVAN FINALY (Chem. Abstr.).

Antabuse and the Metabolism of Alcohol. Newman, Henry W. (*Stanford Univ. School of Med., San Francisco*). [*Calif. Med.*, **73**, 137–40 (1950).]

Two dogs which received orally 0·5 gm. antabuse (I) (tetraethylthiuram) on the first day, 0·25 gm. on the 2nd, and 0·125 gm. daily for a week showed after injection of 1 gm./kgm. EtOH a normal blood concentration of EtOH, while their blood acetyldehyde (II) went up irregularly to 0·6 gm./100 c.c. Upon infusion of 185 mgm./kgm. (II), blood (II) increased to 2·0–4·0 mgm. Conclusion : (I) slows down the metabolism of (II). F. FROMM (Chem. Abstr.).

Antabuse Therapy in Chronic Alcoholism. Dale, Paul W., and Ebaugh, Franklin G. (*Univ. of Colorado School of Medicine, Denver*). [*Am. J. Med. Sci.*, **220**, 103–9 (1950).]

A review of previous literature and a report of a new series of 29 cases in which "recovery" occurred in 9 and some improvement in 12. The action of tetraethylthiuram disulfide (antabuse) in producing unpleasant symptoms in persons taking alcohol is apparently due to formation of high blood levels of AcH from the alcohol. Caution is recommended, since several deaths have been reported during the course of an antabuse-alcoholic reaction. although few untoward reactions to antabuse alone have occurred. MARION HORN PESKIN (Chem. Abstr.).

Effect of Tetraethylthiuram Disulfide (*Antabuse*) *on Metabolism of Lactic Acid in the Human Organism. Jokivartio, E.* (*Univ. Helsinki, Finland*). [*Acta Pharmacol. et Toxicol.*, **6**, 107–14 (1950).]

Treatment with antabuse prevented to a considerable but variable extent the rise in blood lactic acid which usually follows heavy muscular work by alcoholics and non-alcoholics. L. E. GILSON (Chem. Abstr.).

New Parasympathetic Stimulant (*Ethyl 3,3-Dimethyl-5-allylbarbituric Acid*). *I. Its Effect on Gastric Secretion. Ballem, C. M., Noble, R. L., and Webster, D. R.* (*Can. Med. Assoc. J.*, **58**, 447–50 (1948).]

Na ethyl 3,3-dimethyl-5-allylbarbituric acid is a powerful stimulant to gastric secretion in dogs. The injection of 4 gm. per kgm. of body-weight, subcutaneously, in a 36-kgm. dog caused secretion of juice with a pH of 1·4 at the rate of 462 ml. per hour. The main action is on the acid- and mucus-producing cells, with a less marked action on the peptic cells. The action is central and is prevented by vagotony, tetraethylammonium chloride, or nembutal anesthesia. There is also an apparent paralysis of the nictitating membrane and reaction of the pupil, suggesting a depression of sympathetic function. Larger doses are followed by symptoms of excitement and inco-ordination. B. A. (Chem. Abstr.).

Action of Various Barbiturates on the Parenchymatous Organs in Narcosis of Long Duration. Carlon, C., and Mondini, P. (Univ. Padova, Italy). [*Giorn. ital. anestesiol.*, **15**, 282–6 (1949).]

Guinea-pigs were narcotized with farmotal, thionarcon or narconumal, with doses progressively less with time. Observations were made on liver, kidney and spleen for narcoses of 1–3 hours. Especially the liver and kidney showed diffuse congestion and degeneration of the epithelium. Narcosis with farmotal was rapid and profound, with no muscular tremor; breathing was faster, and respiration arrested after 120–150 minutes. Thionarcon gave superficial sleep even after 2–3 hours, and the animals reacted well to stimuli. With larger doses breathing was slowed down and respiration paralyzed. Narconumal was less toxic; narcosis was sufficiently deep but brief. Diffuse muscular tremors were observed. The animals breathed normally, but reacted to pain a few minutes after injection.

M. Elliott (Chem. Abstr.).

Pain Relief with Hypnotic Doses of Barbiturates, and a Hypothesis. Keats, Arthur S., and Beecher, Henry K. (Harvard Univ. Med. School. Boston). [*J. Pharmacol. Exptl. Therap.*, **100**, 1–13 (1950).]

Chiefly discussion. Hypnotic doses of pentobarbital-Na given intravenously relieved post-operative pain in 50 per cent. of the patients treated. A hypothesis is presented to explain the analgesic properties of pentobarbital by depression of internuncial spread of pain impulses in the brain, and inhibition of the psychic phase of pain experience. L. E. Gilson (Chem. Abstr.).

Rate of Penetration of Barbituric Acid Derivatives into the Brain. Butler, Thomas C. (Johns Hopkins Univ., Baltimore, Md.). [*J. Pharmacol. Exptl. Therap.*, **100**, 219–26 (1950).]

After intravenous injection of barbital and hexethal (ortal) in mice, the concentrations in the brain were determined by ultraviolet spectrophotometric methods which are described in detail. The concentration of barbital in the brain rises gradually for a considerable time after the injection. The increasing concentration corresponds closely with the increasing intensity of neurological effects. Hexethal, which shows immediate onset of anesthetic effects, attains its maximum concentration in the brain very quickly. It appears that the wide differences among the 5,5-disubstituted barbiturates with respect to the rate of onset of effects after intravenous injection are attributable to differences in rates of penetration into the brain. L. E. Gilson (Chem. Abstr.).

The Excretion of Barbituric Acids during Continued Sleep Treatment of Schizophrenia. Staub, H. (Univ. Zurich, Switz.). [*Schweiz. Arch. Neurol. Psychiat.*, **65**, 330–70 (1950).]

As a treatment for schizophrenia various mixtures of barbital (I), phenobarbital (II), allobarbital (III), and sandoptal (IV), with and without urethan, novalgin, sympathol, dionine and scopolamine-HBr, were used, usually by intramuscular injection, to induce deep (6 cases), or twilight (3 cases) sleep, continued for periods of 12–14 days, except for one 9-day and one 28-day treatment. The excretion of (I), (II), (III) and (IV) in the urine was determined throughout the periods of treatment and for several days after. The urine was acidified, if necessary, with AcOH, concentrated in vacuum to a syrup, and extracted with EtOAc. The extract was evaporated, dissolved in a little water, acidified, saturated with NaCl, and extracted with Et_2O, which was evaporated. The residue was dissolved in 10 per cent. NaOH and extracted with Et_2O to remove alkaloids and neutral substances. The alkaloid solution was acidified with HCl, saturated with $NaHCO_3$, and extracted with Et_2O. The dried extract was sublimed in vacuum at 120–130°, and the crystal sublimate was dissolved in water. The solution was extracted with Et_2O, which was evaporated. The residue was weighed as total barbiturates (V). The unsaturated (III) or (IV) (they were not given together), was removed by chromate oxidation of the mixture, (I) and (II) were extracted, purified as before, and distilled by comparison of the m.p. with m.ps. of known mixtures of pure (I) and (II). The daily excretion of (V) was closely related to the volume of urine. There were wide variations in the percentages of the daily dose of (I), (II), (III) and (IV)

excreted. The excretion in the after period varied widely among patients, but usually continued for several days. The total excretion for the entire period was about 70 per cent. of the amount given for (I), 40 per cent. for (III), and 20 per cent. for (II) and (IV). The findings are discussed in detail in relation to the type of therapy and the effect of alkaloids and other drugs.

The Distribution of Barbituric Acids in the Organism of Mentally Diseased Patients during Sleep Therapy. [*Ibid.*, 371–80.]

(V), (I), (II) and (III) were determined in some or all of 14 organs, blood, bile and bladder urine from three patients who had died during sleep therapy with a mixture of (I), (II) and (III) (*cf. C. A.*, **40**, 402[9] and above for methods used). Concentrations of each barbiturate tended to be similar in different organs of the same patient, but there were some exceptions. The lowest concentration of (I), (II) or (III) was 1·1 mgm., and the highest 17·4 mgm. per 100 gm. In one patient a concentration of 40·6 mgm. (V) per 100 gm. was found in the liver. Concentrations in the brain were generally similar to those found in other organs. The results are compared with the dosage of (I), (II), (III) and (IV), which had been given. WARREN N. SPERRY (Chem. Abstr.).

The Enzymic Mechanism of Barbiturate Action. Persky, H., Golstein, M. S., and Levine, R. (Michael Reese Hosp., Chicago). [*J. Pharmacol. Exptl. Therap.*, **100**, 273–83 (1950).]

The effect of pentobarbital on various enzyme systems was studied *in vitro*. Pentobarbital was shown to block the pyruvic acid oxidase system, most likely at the oxidation of the 2-carbon fragment. It does not block the oxidation of flavoprotein by either O or cytochrome c. It apparently blocks the essential SH groups of the dehydrogenase of the pyruvic acid system. The relation of this enzyme inhibition to narcosis *in vivo* is discussed.

L. E. GILSON (Chem. Abstr.).

Anti-convulsant Drugs. III. Some Allophanates. Spielman, M. A., Barnes, J. D., and Close, W. J. (Abbott Labs., North Chicago). [*J. Am. Chem. Soc.*, **72**, 2520–2 (1950); *C. A.*, **43**, 2169c.]

Thirty-six esters of allophanic acid were prepared and tested for anti-convulsant activity. The most active compounds were those derived from secondary and tertiary alcoholics of 5–7 C. The allophanates were mild hypnotics. HCNO was prepared by subliming $(HNCO)_3.2H_2O$ and passing same through a Pyrex tube in electric combustion furnace at dull, red heat, and then leading HCNO directly into the alcohol. A gentle current of CO_2 was used. Reaction required about 15 minutes. Receiver was removed, stoppered, and let stand 24 hours or longer, allophanate filtered and washed with little Et_2O, and crystallized from EtOH previously saturated with CO_2. Carbamates, as by-products, in part, caused low yields. A second method was illustrated by the addition to glacial AcOH and tertiary $C_5H_{11}OH$ of KCNO, portion-wise with stirring. Temperatures rose to 50° and then subsided. After standing several hours, mixture was diluted with H_2O and extracted with Et_2O, Et_2O washed with H_2O and evaporated and residue crystallized from EtOH, yielding tert-amyl allophanate, m. 166–8°. Results from KCNO were in general erratic and 3-Me-2-C_4H_9OH gave only carbamate. Anti-convulsant tests in mice were made by electroshock or by injection of metrazole in graded oral doses, usually 200, 400 and 800 mgm./kgm. Their low toxicity was evident in the virtual absence of any effects except depression. The compounds prepared were moderately hypnotic. None were considered worthy of clinical trial.

R. E. DUNBAR (Chem. Abstr.).

Effect of Convulsant and Anti-convulsant Agents on the Activity of Cytochrome Oxidase. Torda, Clara, and Wolff, Harold G. (Cornell Univ., Med. Coll., New York, N.Y.). [*Proc. Soc. Exptl. Biol. Med.*, **74**, 744–6 (1950).]

The activity of cytochrome oxidase preparations from rat liver or brain was considerably increased in the presence of the convulsant agents, acetylcholine, caffeine, camphor, DDT, Me salicylates, metrazole, picrotoxin, scilliroside and strychnine, in concentrations of 10^{-5} to 10^{-3} M. The activity was not significantly

modified by choline or the anti-convulsant agents, hydantoin, methylphenylethylhydantoin, phenobarbital, Na phenylhydantoinate, and tridione, in 10^{-3} M and lower concentrations. Convulsant agents, therefore, activate at least two processes, a monoxidative mechanism that initiates the seizures and the oxidative recovery processes occurring during the convulsive seizures.

L. E. Gilson (Chem. Abstr.).

The Site of Action of Metrazole and Coramine. V. The Contrasting Basic Vegetative Action of both Drugs. Hahn, Fritz, Muller, Dieter, and Rummel, Walter (Med. Akad. Dusseldorf, Ger.). [*Arch. exptl. Path. Pharmakol.*, **209**, 312–24 (1950); *cf. C. A.*, **43**, 7137*e*.]

Frogs receiving coramine (I) in doses of 0·6 to 2·0 gm./kgm. were apathetic and flaccid with occasional convulsions. Their melanophores were dilated. Frogs receiving metrazole (II) in doses of 80–100 mgm./kgm. were active and excitable and their melanophores and skin muscles contracted. The effect of (I) on the melanophores was counteracted by (II) and adrenaline. N,N-diethy-3,5-dimethyl-4-isoxazol carboxamide and N,N,N′,N′-tetraethylphthalamide had a (I)-like action on the melanophores, while 4-cyclohexyl-3-ethyl-4,1,2,-triazone and pyramidone acted like (II) (IV).

VI. The Mechanism of the Blood Pressure Effect of Central Analeptics. Fritz, Hahn, and Rummel, Walter (Pharmakol. Inst. Med. Akad., Dusseldorf, Ger.). [*Ibid.*, 325–39.]

Metrazole (I) injections into the vertebral artery of cats anesthetized with 5 per cent. chloralose in 25 per cent. urethan, after vagotomy and severing of the carotid sinus nerves, produced no regular increase in blood pressure as seen after intravenous injections. Very often the effect was hypotonic and the hypertonic response either preceded or followed the hypotonic one. The equilibrium of the blood pressure regulating center in the medulla was considered responsible for the effect of an intravertebral injection of (I). Coramine (II) had a hypotonic effect after intravenous or after intravertèbral injection. The effect of (II) probably is also referable to the blood pressure regulating center in the medulla. An initial hypertonic effect after intervertebral injection is more often seen with (II) than with (I), while the late hypertonic effect is rare and weak with (II). Picrotoxin and triazole derivatives behaved like (I). Caffeine and hexetone had no hypotonic action after intravenous injection. Richard F. Riley (Chem. Abstr.).

A Comparison of the Anti-convulsant Action of Some Phenylhydantoins and their Corresponding Phenylacetylureas. Swinyard, Ewart A., Toman, James E. P., Jolley, Joel M., and Henrie, Madge (Univ. of Utah, Salt Lake City). [*J. Pharmacol. Exptl. Therap.*, **100**, 151–7 (1950).]

Phenylacetylurea and its homologs with Me, Et and Ph substituted on the α-*C* of the phenylacetyl group, and the corresponding phenylhydantoins were compared with respect to solubility in water, minimal neurological toxic dose in rats, ability to modify maximal electroshock seizure, anti-metrazole potency in rats, and ability to suppress induced hyperexcitability and hyperresponsiveness in frog sciatic nerve. All the compounds showed some anti-convulsant potency except the very insoluble diphenylacetylurea. There was no close correlation between solubility and pharmacological properties. The hydantoins were much more soluble than the phenylacetylureas. There was no remarkable difference in the toxicities and relative anti-metrazole activities of the two series. L. E. Gilson (Chem. Abstr.).